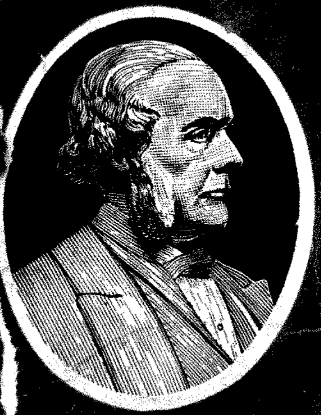

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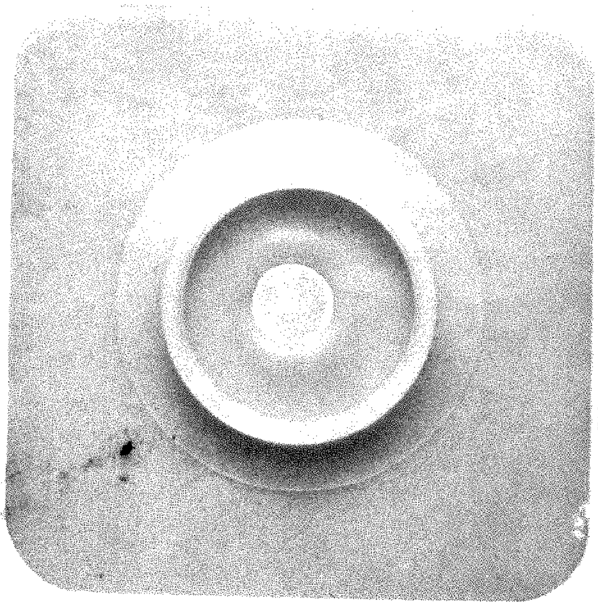

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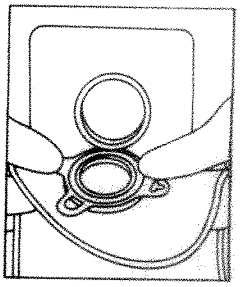

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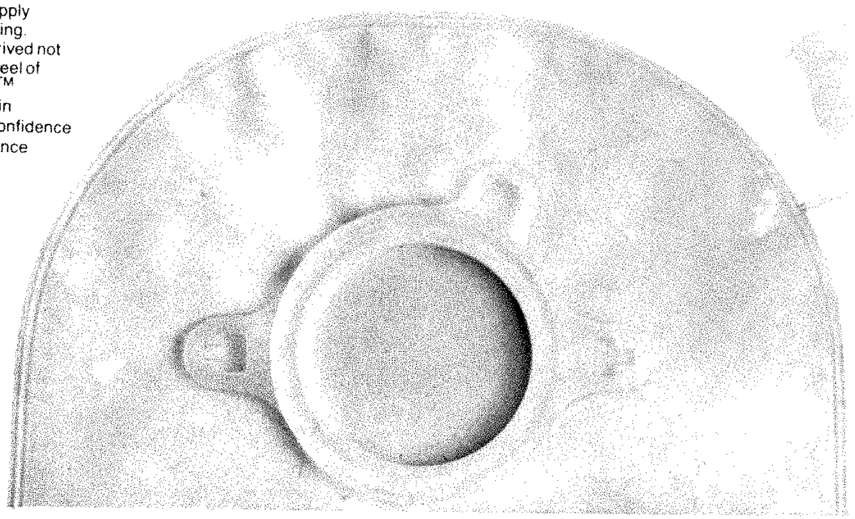

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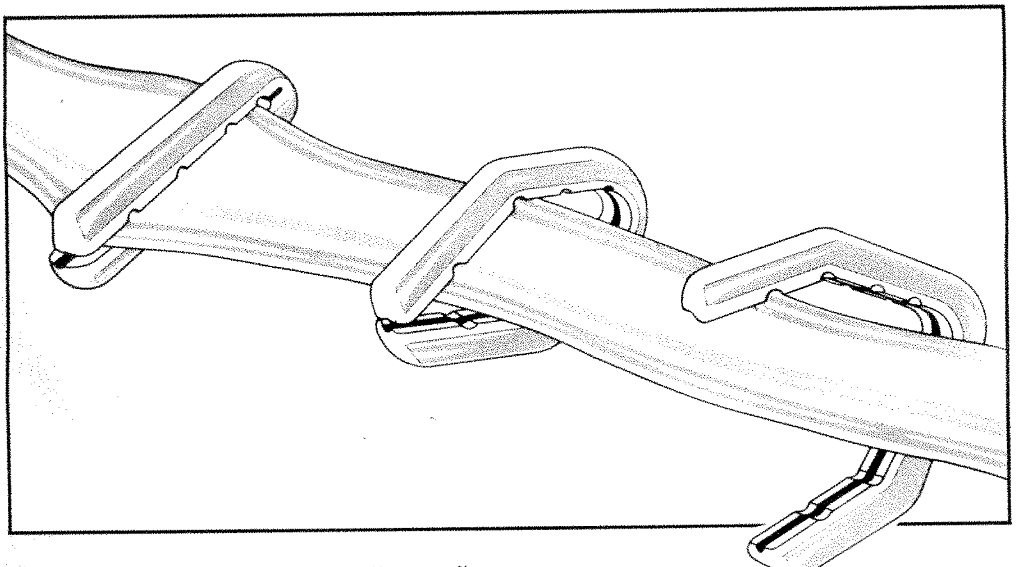

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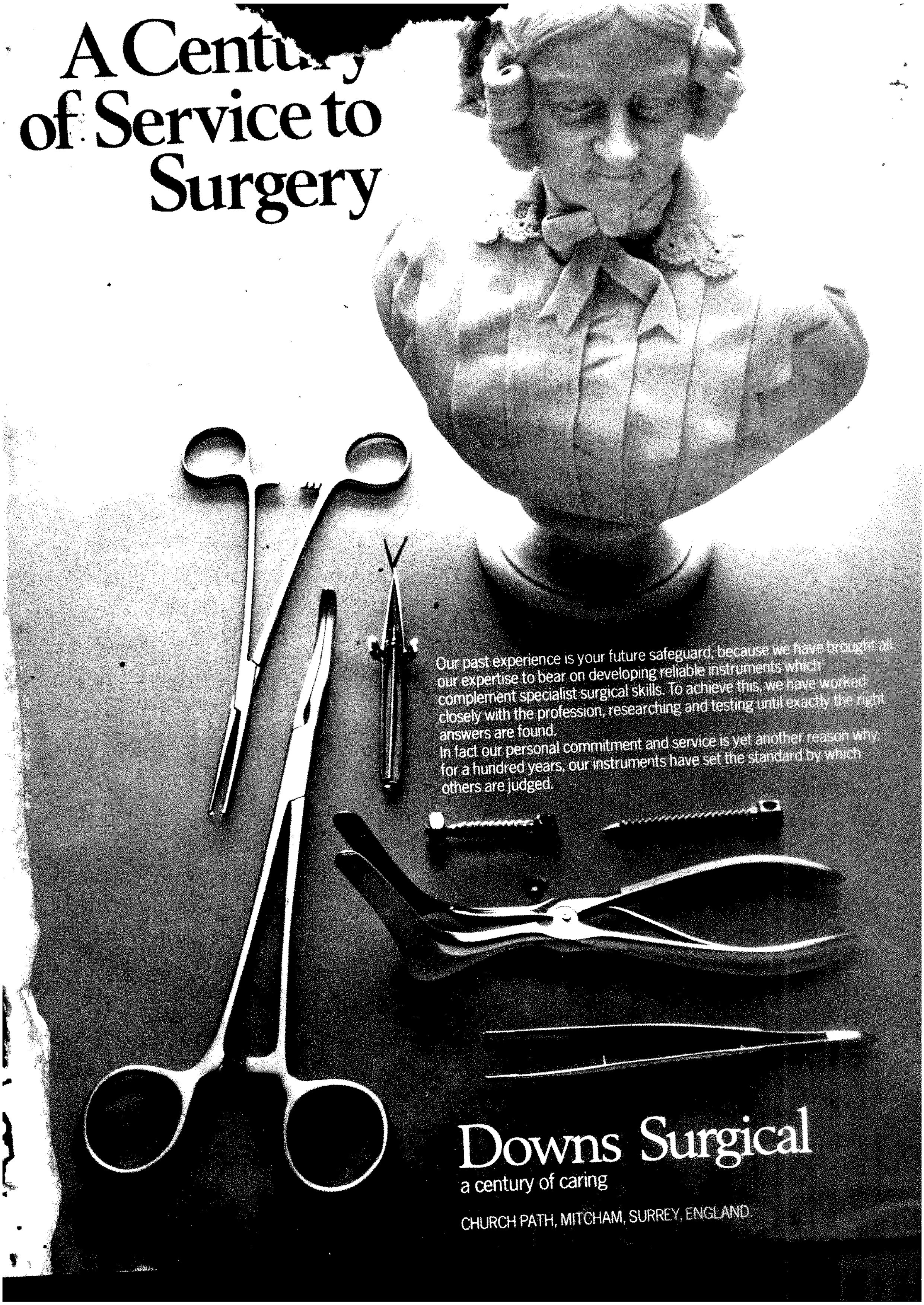

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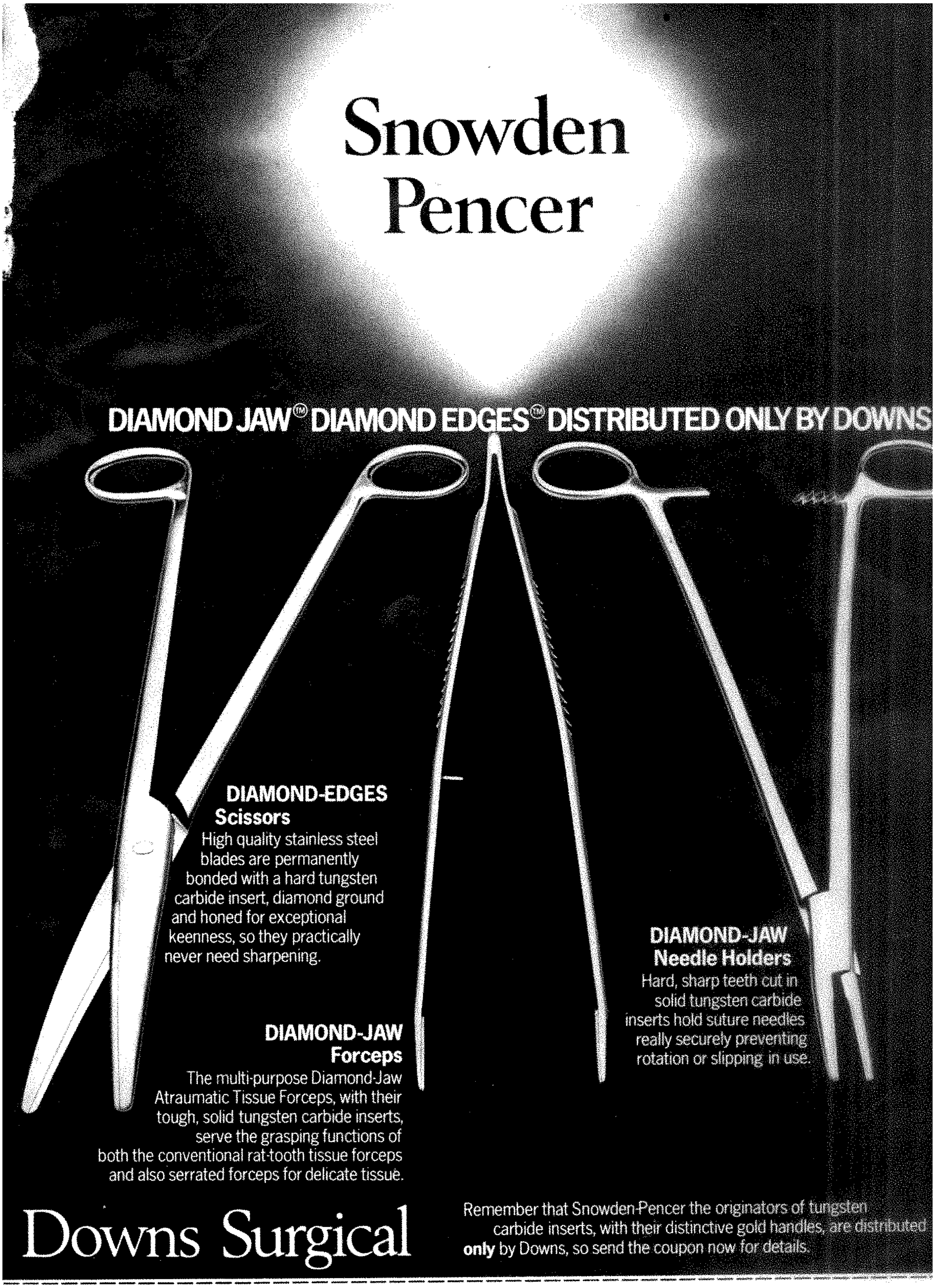

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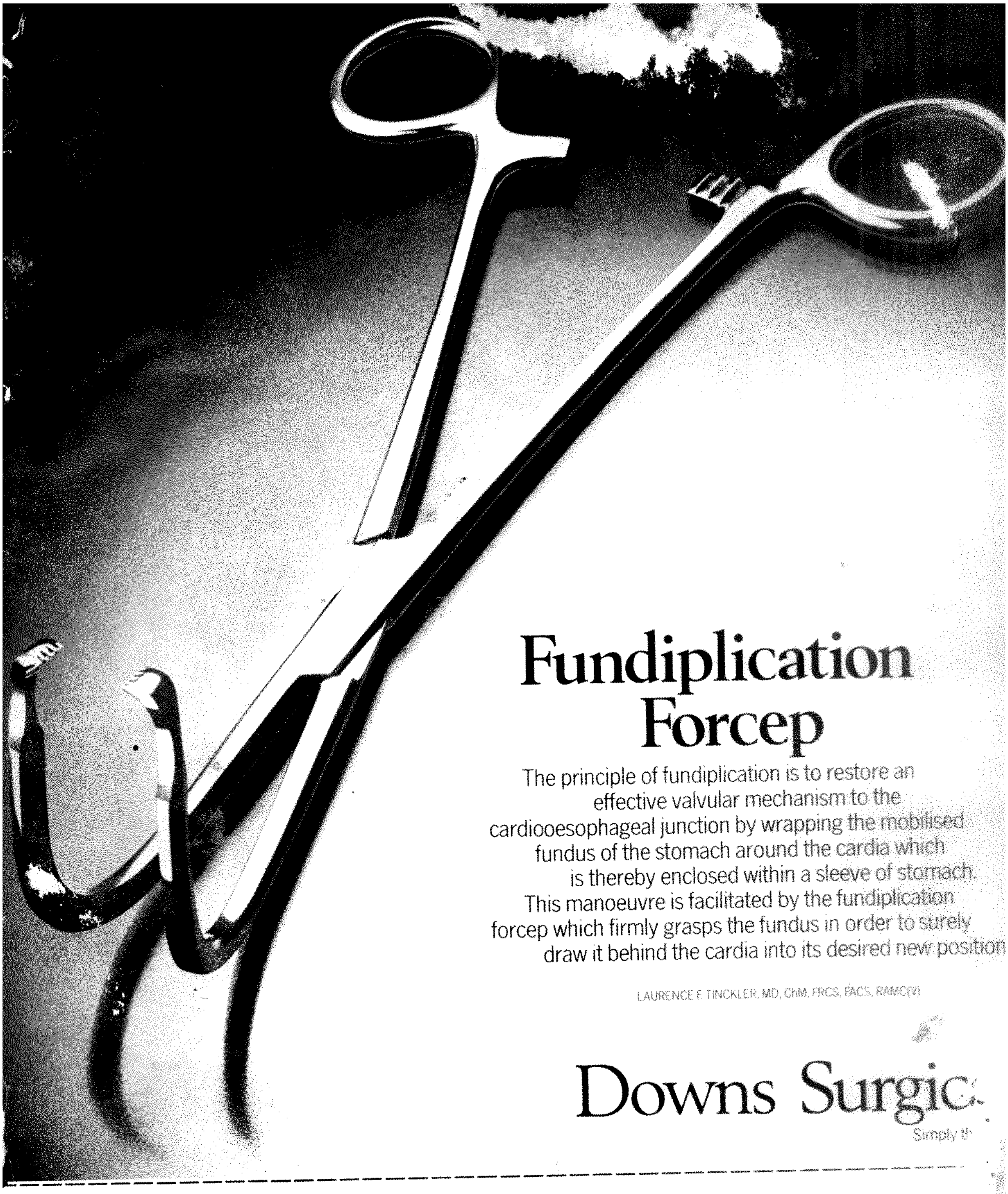

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The British Journal of Surgery

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A curious occipital polyp

M. GABER*

SUMMARY

Muscles which lose their attachments are uncommon. During development this normally occurs in certain muscles, e.g. the muscles of the face and epicranius; these muscles lose their skeletal connections before migration. In the case presented here a muscle in the occipital region had lost its attachment and formed a peculiar swelling.

Case report

A 6-year-old girl presented with an occipital pedunculated swelling 5 cm long (*Fig.* 1) which moved up and down during mastication (*Fig.* 2). No other movements of the face, neck or the tongue caused such a movement. The swelling was present at birth and continued to grow slowly with the child.

The swelling was excised. During dissection a muscle was seen attached to the external occipital protuberance. On section the muscle was found to be inserted into the skin at the apex of the swelling, causing corrugations of the skin (*Fig.* 3).

Histological section showed striated muscle with a tendinous end in the centre of fibro-fatty tissue. Nerve fibres were also seen (*Fig.* 4).

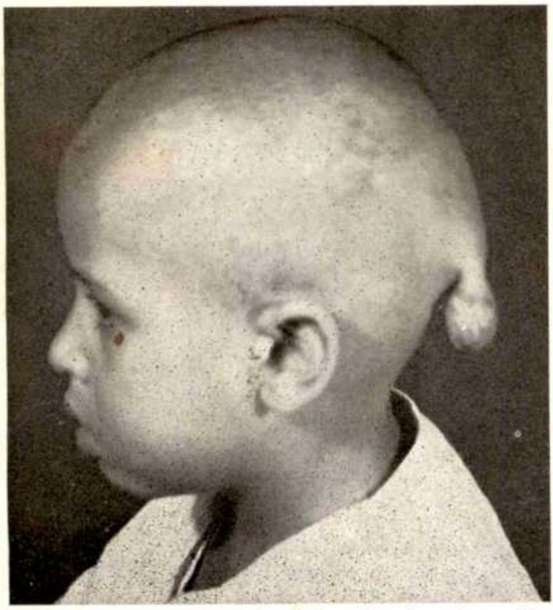

Fig. 1. The patient with the head shaved to show the swelling.

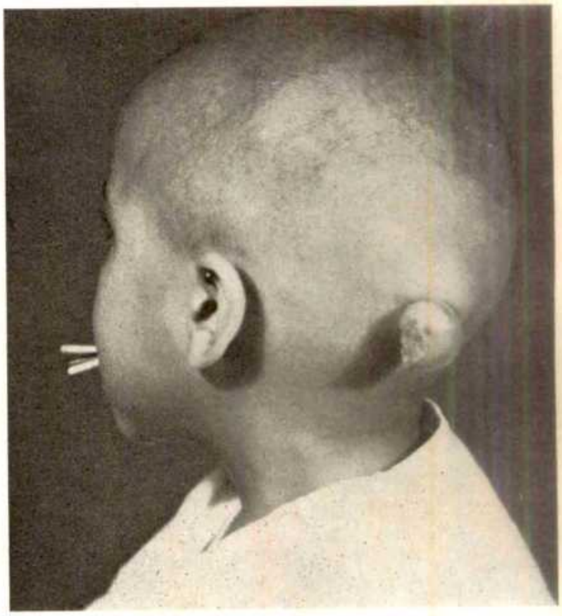

Fig. 2. Showing the movement of the swelling on mastication.

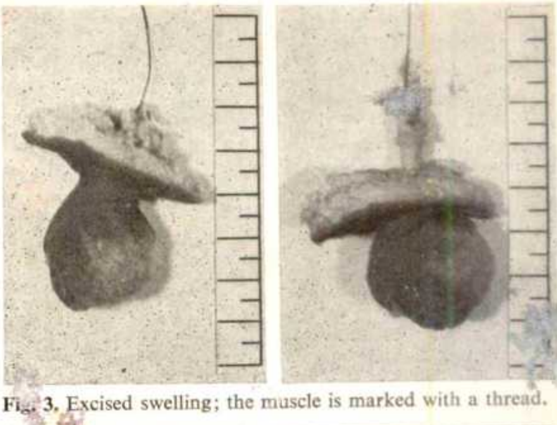

Fig. 3. Excised swelling; the muscle is marked with a thread.

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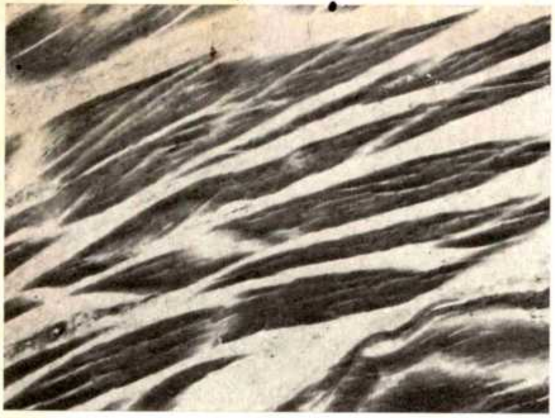

Fig. 4. Histological section showing the muscle. (HE. × 60.)

Discussion

The muscle mentioned in this case could be the transversus nuchae muscle, which is present in 25 per cent of the population. It takes origin from the external occipital protuberance and frequently is inserted with the auricularis posterior muscle. It is supplied by the occipital division of the posterior auricular branch of the facial nerve. The muscle in this case may have had a common innervation with the buccinator muscle, which is also supplied by the facial nerve. If so, this would explain the movement of the swelling during mastication.

Muscles of the tongue develop in the occipital region before migration; the possibility of the muscle mentioned in this case being a detached part of this group of muscles is remote.

Bibliography

AREY L. B. (1974) *Developmental Anatomy*, 7th ed. Philadelphia, Saunders, p. 234.

Gray's Textbook of Anatomy (1972) 34th ed. London, Longmans, p. 593.

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Br. J. Surg. Vol. 66 (1979) 3–4

Spinal epidural abscess presenting as acute abdomen in a child

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SUMMARY
Spinal epidural abscess is seldom encountered in children and rarely occurs in the absence of spinal pain. A case is described in which a child with a thoracic epidural abscess presented with abdominal rather than spinal pain. Thoracolumbar radicular inflammation and visceroparietal reflexes initiated by a 'spinal ileus' probably produced the symptoms and signs of acute intra-abdominal disease. Consideration of intraspinal disease is advisable in all cases of acute abdomen which exhibit atypical features.

MOST paediatric surgeons have little experience with spinal epidural abscesses since these lesions account for only 0·2–1·2 of every 10 000 general hospital admissions (Baker et al., 1975) and less than 1·5 per cent of the reported cases involve children (Davidson and Zajac, 1978). Fortunately, the early signs and symptoms of this disease usually direct the surgeon's attention to the spine before permanent motor and sensory paralysis supervenes. Spinal pain is the most important initial complaint (Messer et al., 1977) and was mentioned by all 20 patients reported by Heusner (1948), by all 39 reported by Baker et al. (1975) and by all 49 reported by Hancock (1973). In addition, local tenderness was elicited by spinal percussion in 90–100 per cent of these cases. Early diagnosis may be almost impossible when local spinal pain is inconspicuous or absent (Ashby, 1977), when toxic epiphenomena divert attention from subtle signs of neurologic dysfunction and when the patient is an acutely distressed and uncooperative child. The following case is unusual in that it involved a child in whom a history of spinal pain was not obtained and the clinical presentation was that of acute intra-abdominal disease.

Case report

A 7-year-old girl developed malaise, anorexia and dysuria 6 days before the eventual hospital admission. She subsequently complained of aching over the anterior aspect of both thighs. Two days before admission she developed constant central abdominal pain and intermittent vomiting. She had a single, normal bowel movement during this 6-day period. At no time did she complain of back pain.

On examination the child appeared toxic and anxious. The blood pressure was 100/60 mmHg, the heart rate 130/min and the oral temperature 38·4 °C. The entire abdomen was distended and resonant. There was generalized tenderness and guarding, but these signs were more prominent in the right lower quadrant. Only mild tenderness was elicited on digital rectal examination. Bowel sounds were normal in pitch but decreased in frequency.

The haemoglobin was 10·2 g/dl, the white blood cell count 16×10^9/l and the erythrocyte sedimentation rate (Wintrobe) 58 mm/h. Urinalysis demonstrated 3 leucocytes per high-powered field. Urine culture was sterile. Serum electrolytes, urea and creatinine were all normal. Abdominal X-rays revealed gaseous distension of both the large and small bowels with several fluid levels.

The patient underwent laparotomy on the night of admission in order to exclude appendicitis. A large volume of non-purulent, free peritoneal fluid was encountered (which subsequently proved to be sterile). The entire bowel was dilated but otherwise normal. The appendix was not grossly inflamed. The retroperitoneal tissues also appeared normal. Needles were inserted into the psoas muscles but no pus could be aspirated.

The following morning the patient was afebrile. She continued to complain of bilateral anterior thigh pain and developed cutaneous hyperaesthesias over these areas. Both groins were tender to palpation. Late in the day she became incontinent of urine. On the morning of the second postoperative day the nurse noted that the child did not move her legs when she was placed on the bed pan.

Examination at that time disclosed a flaccid paraplegia. Deep tendon reflexes were difficult to obtain and plantar reflexes could not be elicited. Hypoalgesia to pin-prick was present to the level of the umbilicus (T10). Because of nuchal rigidity and headache, a lumbar puncture was performed at the L3–4 interspinous space. Viscous, yellow cerebrospinal fluid was obtained, but the flow soon ceased. Yellow–green pus (10 ml) was aspirated from the epidural space as the needle was withdrawn. A Gram stain demonstrated clumps of Gram-positive cocci. *Staphylococcus aureus* resistant to penicillin was cultured from both the spinal fluid and the epidural pus. The cerebrospinal fluid had a glucose content of 1·2 mmol/l (normal 2·8–5·6) and contained 22 polymorphonuclear leucocytes and 14 lymphocytes per cubic millilitre.

The patient was given intravenous gentamicin and cloxacillin and was transfered to the neurosurgery service at Plymouth General Hospital. The midthoracic spinous processes were found to be tender to palpation. Plain X-rays of the entire spinal column showed no signs of osteomyelitis. A cisternal myelogram demonstrated a complete subarachnoid block at the T4 level. Less than 6 h after she was first noted to be paraplegic, the patient underwent a T4 laminectomy. More than 20 ml of pus were evacuated from the epidural space. Rubber catheters (8 Fr.) were inserted rostrally and caudally into the spinal canal and were brought out through a separate skin incision. The laminectomy incision was closed primarily.

The epidural space was irrigated every 6 h with a solution containing cloxacillin (1 g/100 ml) which was instilled through the catheters. The catheters were removed after 5 days. The patient received flucloxacillin (1 g/d) parenterally for 10 days and then orally for 4 weeks. A myelogram on the seventh postoperative day was normal.

The patient gradually regained lower extremity strength and bowel and bladder continence. Two months after laminectomy she was fully ambulatory, and motor, sensory and reflex examinations were normal.

Discussion

No spinal cause of acute abdominal pain in children was encountered in a recent clinical series reported by Jones (1976) or in an earlier one reported by Winsey and Jones (1967). However, Cope (1972) notes that abdominal pain is a frequent symptom of vertebral osteomyelitis in children and he advocates inspection and palpation of the spine in those cases of abdominal pain in which diagnosis remains in doubt. The relatively high incidence of laparotomy in spinal diseases that present atypically with major abdominal complaints probably indicates that this suggestion is

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often overlooked (Sullivan and Symmonds, 1964; Watkin, 1970).

Suspicion should be raised by even minor symptoms that are not typical of intra-abdominal disease. For example, our patient complained of anterior thigh pain and paraesthesias, which were probably due to inflammation of upper lumbar nerve roots. She also had a persistent headache, which is common with spinal epidural abscess (Heusner, 1948; Baker et al., 1975) but is infrequent with intra-abdominal disease (Winsey and Jones, 1967). Urinary incontinence (or retention) often adumbrates motor and sensory paralysis, which may occur abruptly and then be only partially reversible. In addition to spinal tenderness, examination during the pre-paralytic phase of spinal cord compression often discloses hyperactive reflexes in the lower extremities and extensor plantar reflexes. Diagnosis and treatment during the pre-paralytic phase are of critical importance since the degree of residual functional impairment is directly related to the degree and duration of the preoperative neurological deficit (Heusner, 1948).

Spinal epidural abscess and intra-abdominal sepsis may occasionally coincide since infection may spread haematogenously via veins that connect the epidural space with the thoracoabdominal wall and with the retroperitoneum (McLaurin, 1967). In addition, an epidural abscess may extend through intervertebral foramina and along spinal nerves to produce a perinephric abscess (Stammers, 1938). In this case, however, laparotomy excluded these possibilities. Therefore, the patient's signs and symptoms were probably referable to disturbances in the innervation of the abdominal wall and viscera. Abdominal pain, rigidity and local tenderness may be caused by inflammation of the lower thoracic nerve roots which supply the abdominal wall (Sullivan and Symmonds, 1964). These signs and symptoms are more commonly due to visceroparietal reflexes which are caused by visceral dysfunction. Intraspinal disease may not only enhance these reflexes (Ashby, 1977) but may also produce a 'spinal ileus' which initiates them (Watkin, 1970). This syndrome of colicky abdominal pain associated with gaseous distension of the bowel and variable changes in bowel sounds may be encountered in a variety of spinal lesions, including fractures, herniated intravertebral discs and spinal cord infarcts (Watkin, 1970). The pathogenesis of this syndrome remains unclear, but probably involves an acute imbalance between the sympathetic and vagal innervations of the bowel (Morton et al., 1960).

Acknowledgement

We wish to thank Dr M. A. Voyce, Consultant Paediatrician, who kindly referred this case to us.

References

ASHBY E. C. (1977) Abdominal pain of spinal origin. *Ann. R. Coll. Surg. Engl.* **59**, 242–246.

BAKER A. S., OJEMANN R. G., SWARTZ M. N. et al. (1975) Spinal epidural abscess. *N. Engl. J. Med.* **293**, 463–468.

COPE Z. (1972) *The Early Diagnosis of the Acute Abdomen*, 14th ed. London, Oxford.

DAVIDSON R. I. and ZAJAC J. J. (1978) Spinal epidural empyema with Brown-Sequard syndrome. *Surg. Neurol.* **9**, 195–197.

HANCOCK D. O. (1973) A study of 49 patients with acute spinal extradural abscess. *Paraplegia* **10**, 285–288.

HEUSNER A. P. (1948) Non-tuberculous spinal epidural infections. *N. Engl. J. Med.* **239**, 845–854.

JONES P. F. (1976) Active observation in the management of acute abdominal pain in childhood. *Br. Med. J.* **2**, 551–553.

MCLAURIN R. L. (1967) Spinal suppuration. *Clin. Neurosurg.* **14**, 314–336.

MESSER H. D., LENCHNER G. S., BRUST J. D. M. et al. (1977) Lumbar spinal abscess managed conservatively. Case report. *J. Neurosurg.* **46**, 825–829.

MORTON J. H., SCHWARTZ S. I. and GRAMIAK R. (1960) Ileus of the colon. *Arch. Surg.* **81**, 425–434.

STAMMERS F. A. R. (1938) Spinal epidural suppuration, with special reference to osteomyelitis of the vertebrae. *Br. J. Surg.* **26**, 366–374.

SULLIVAN C. R. and SYMMONDS R. E. (1964) Disk infections and abdominal pain. *JAMA* **188**, 655–658.

WATKIN D. F. L. (1970) Spinal ileus. *Br. J. Surg.* **57**, 142–148.

WINSEY H. S. and JONES P. F. (1967) Acute abdominal pain in childhood: analysis of a year's admissions. *Br. Med. J.* **1**, 653–655.

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Toxic dilatation of the colon in salmonella colitis and inflammatory bowel disease

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SUMMARY

Toxic dilatation of the colon may be due to inflammatory bowel disease, either ulcerative colitis or Crohn's disease of the colon, but recent experience has shown that infective colitis due to salmonella can produce this complication. We present 13 cases with toxic dilatation (9 inflammatory bowel disease and 4 salmonellosis) and outline the diagnostic features and treatment in these patients. It is important to distinguish salmonellosis at an early stage because, whilst toxic dilatation in inflammatory bowel disease is an absolute indication for surgical treatment, cases with this complication due to salmonellosis may be treated conservatively in the majority of instances.

FOR many years gross dilatation of the colon due to inflammation was thought to be a complication which only occurred in ulcerative colitis (Marshak et al., 1950; Brooke and Sampson, 1964). More recently, the complication has been recognized in Crohn's disease of the colon (Turnbull et al., 1970).

Mandal and Mani (1976) demonstrated that salmonella infection commonly produces invasive changes in the colon, and confirmation of their findings was quickly reported from South Africa (Appelbaum et al., 1976) and from Yugoslavia (Radsel-Medvescek et al., 1977). This invasive change may, at times, be severe enough to produce toxic dilatation of the colon (Boyd, 1976; Mandal and Mani, 1976). The purpose of this paper is to report our experience of this complication in both infective and non-infective inflammatory bowel disease.

Patients and methods

During the years 1974–7, 13 patients presented, either to the regional infectious diseases department for the North-west or to the surgical unit which carries out the operative management, with toxic dilatation of the colon. All the patients included in this series were severely ill with colitis and radiologically had gross dilatation of the colon. In the adults the diameter of the transverse colon varied between 8 and 12 cm and in the one infant in the series (*Case* 13) the dilated transverse colon measured 5 cm. Of these cases, 4 were due to ulcerative colitis, 5 to Crohn's disease of the colon and 4 to salmonellosis. Ten of these patients presented to the infectious diseases unit (3 with ulcerative colitis, 4 with Crohn's disease and 3 with salmonellosis) while the other 3 patients, including 1 case of salmonella infection, presented to the surgical unit. All 9 patients with non-infective inflammatory bowel disease (4 with ulcerative colitis and 5 with Crohn's disease) required surgical treatment by subtotal colectomy and ileostomy. One of the 4 patients with toxic dilatation due to salmonella infection required colostomy but the other 3 patients recovered with medical treatment. *Tables I* and *II* show the clinical and investigatory features in all 13 patients. Since toxic dilatation of the colon due to salmonella infection has only recently been reported, we present the 4 patients in our series in more detail.

Case 10: A 19-year-old man was admitted to the infectious diseases unit with a 7-day history of frequent vomiting and diarrhoea, but the stool contained no blood. He had lost weight during his illness and on admission he looked ill and was pyrexial. The abdomen was grossly distended and tympanitic with scanty bowel sounds and there was slight rebound tenderness in the left iliac fossa. The spleen was palpable. He was clinically dehydrated and biochemical studies showed a sodium level of 117 mmol/l, potassium 2·9 mmol/l, chloride 83 mmol/l and blood urea 5·15 mmol/l. His haemoglobin was 13·3 g/dl and the white cell count was 13·6 × 10^9/l (neutrophils 87 per cent). The straight film of the abdomen revealed gross gaseous distension of the colon. Sigmoidoscopy showed inflamed, oedematous mucosa with absent vascular pattern, and rectal biopsy later revealed oedema of the lamina propria with vascular congestion and haemorrhages. Stool culture grew *Salmonella typhimurium*, phage type I, var. 5.

The patient was treated with intravenous fluid replacement and received systemic chloramphenicol, in view of the possibility of salmonella septicaemia, but this was not confirmed. Over the next 4 days the patient's condition improved steadily with gradual lessening of his abdominal distension and diarrhoea. Following recovery, he has been reviewed periodically for 3 years as an outpatient and has had no further bowel problem.

Case 11: A 56-year-old man was admitted to the infectious disease unit with a 15-day history of profuse diarrhoea, commencing soon after a Spanish holiday. He was having watery diarrhoea six to ten times a day without blood or mucus.

On admission, he was febrile and looked ill. The abdomen was grossly distended and tympanitic, with slight rebound tenderness in the right iliac fossa.

A plain X-ray of the abdomen revealed marked gaseous distension of the colon. Biochemistry showed normal serum electrolytes and a blood urea of 2·66 mmol/l. The haemoglobin was 12 g/dl and the white cell count was 14·200 × 10^9/l (neutrophils 61 per cent). Sigmoidoscopy revealed a generally hyperaemic and granular mucosa and biopsy later showed oedema and an increase in the chronic inflammatory cell population of the lamina propria but no crypt abscess formation. Stool culture grew *Salmonella enteritidis*. The man's symptoms and abdominal distension settled slowly over the next 2 weeks. He received no antibiotic therapy.

Barium enema examination several days after admission still showed some colonic dilatation with an abnormal and irregular mucosal pattern in the descending colon and on the left side of the transverse colon, indicative of ulceration.

On outpatient follow-up there were no bowel symptoms and the results of barium enema examination returned to normal.

Case 12: A 47-year-old female was admitted with increasingly severe watery diarrhoea and colicky abdominal pain for 2 weeks following a holiday in Spain. She was treated at home with antibiotics and three stool cultures sent by her family doctor were negative. On admission she looked ill and dehydrated with a tachycardia of 140/min and blood pressure of 80 mm systolic. Her abdomen was grossly distended and tender.

Serum electrolyte estimation confirmed salt depletion. Plain X-ray showed total colonic gaseous distension, most marked in the right and transverse colon. Sigmoidoscopy showed a red inflamed mucosa with absent vascular pattern but no contact bleeding.

Because of the abdominal distension and marked signs of peritoneal irritation, laparotomy was performed immediately following rehydration with intravenous fluids. The colon was grossly dilated with some thickening in the right and transverse colon with a gangrenous area in the mid-transverse colon 1 cm in diameter. The small bowel was normal. The devitalized area on the transverse colon was exteriorized through a separate

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Table I: CLINICAL FEATURES

				Sigmoidoscopy					
Case no.	Age at onset (yr)/ sex	Total history	Abdominal tenderness	Diffuse	Deep ulcers	Absent vessels	Oedema	Friability	Path
1	12/F	3 wk	+	+	0	+	±	0	Crohn's
3	26/M	2 yr	+	Patchy	±	+	+	+	Crohn's
2	42/F	2 wk	No	+	0	+	+	++	Crohn's
4	21/F	2 yr	++	0	0	0	0	0	Crohn's
5	24/F	1 yr	No	Patchy	+	+	++	++	Crohn's
6	50/F	1 yr	No	+	0	+	++	++	CUC
7	24/M	4 yr	No	+	0	+	++	++	CUC
8	18/M	5 d	+	+	0	+	++	++	CUC
9	22/F	3 wk	No	+	0	+	++	++	CUC
10	19/M	1 wk	±	+	0	+	+	0	*Salmonella*
11	56/M	2 wk	+	+	0	+	+	+	*Salmonella*
12	47/F	2 wk	++	+	0	+	±	0	Salmonella
13	15 mth	3 d	±			Not done			*Salmonella*

CUC, Chronic ulcerative colitis.

Table II: INVESTIGATORY FEATURES

Case no.	Temperature on admission (°C)	Haemoglobin on admission (g/dl)	White cell count on admission (×10⁹/l)	Serum albumin on admission (g/l)	Maximum width of transverse colon (cm)
1	38·6	9·2	17·6	28	9·0
2	37·8	13·2	12·1	38	7·0
3	38·8	10·5	9·6	22	12·0
4	39·6	9·6	30·8	24	8·0
5	40·2	11·2	18·0	23	10·0
6	38·5	10·3	12·9	30	8·0
7	37·0	9·8	14·0	30	8·0
8	37·5	11·2	13·8	27	9·5
9	38·4	11·4	20·0	28	8·0
10	39·0	13·3	13·6	37	10·0
11	39·0	12·0	14·2	28	10·5
12	37·8	10·3	18·2	29	10·0
13	38·5	11·5	18·6	Not done	5·0

incision and a colostomy opened and sutured to the skin. The following day stool culture confirmed salmonella group B and the patient was given a course of chloramphenicol. She recovered steadily and was discharged 18 days after the operation.

Three months later barium studies showed a normal colon and the colostomy was then closed. The patient has remained well for 2 years.

Case 13: A 15-month-old male infant was admitted to the infectious diseases unit with a 10-day history of diarrhoea, not containing any blood. He was not dehydrated and his diarrhoea settled soon after admission. *Shigella sonnei* was isolated from his faeces and initially his appeared to be a case of resolving Sonne dysentery, but 7 days after admission there was a recurrence of fever and severe diarrhoea with rapid distension of the abdomen. Straight X-ray of the abdomen revealed multiple fluid levels in the small intestine and gross distension of the colon.

Further stool cultures now yielded *Salmonella typhimurium*, presumably due to cross-infection, thus explaining the severe recurrence of symptoms. The child gradually improved over the next few days with intravenous fluid therapy and he has remained quite well since.

Differentiating features

History and examination

It may be difficult to distinguish acute colitis due to salmonella infection from that due to non-infective inflammatory bowel disease. Both conditio diarrhoea of similar severity, leading to electrolyte depletion with tachycardia tension. The history of a recent Mec holiday or a history of less than 2 weeks' suggestive of salmonella infection whereas matory bowel disease the recent history longer and often there is a history of previo

Blood in the stool may be a striking featu cases of salmonella infection, but more us is absent from the stool (Mandal and M In this study, none of the 4 cases of salmon blood in the stool but bleeding was us inflammatory bowel disease cases.

When toxic dilatation is present the a distended, and in the salmonella infectio this series tenderness was always present was absent in several cases of inflammat disease. Two cases of the latter did hav abdominal masses.

Sigmoidoscopy

The appearances in both ulcerative c salmonella colitis showed diffuse inflammat ment of the rectum with spontaneous oedema and pus, and therefore did n distinguish the two conditions. In Crohn the proctitis may be of similar type but may be relatively spared or contain linear this was found in several cases. Thus, in sigmoidoscopy had a useful discriminator identifying Crohn's disease in several of th

Biopsy

This is quite a useful procedure in diff salmonella colitis from inflammatory bo (Day et al., 1978); however, it played rela part in the urgent management of these pa toxic dilatation because a decision had t regarding urgent surgery before the biops processed.

Stool culture

Repeated stool cultures are of considerable i in all patients presenting with bloody diarr of a persistent nature. Early specimens negative if the patient has received anti happened in *Case* 12.

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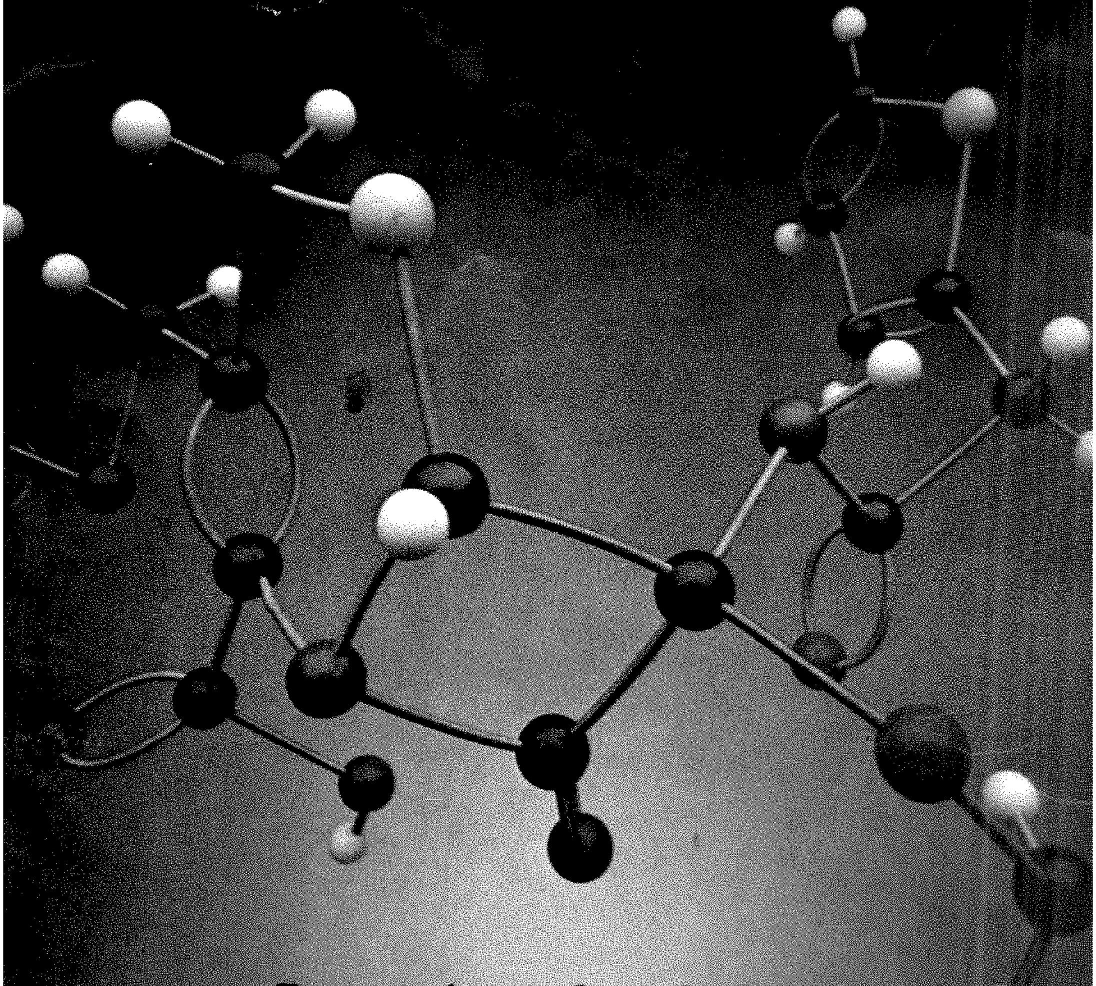

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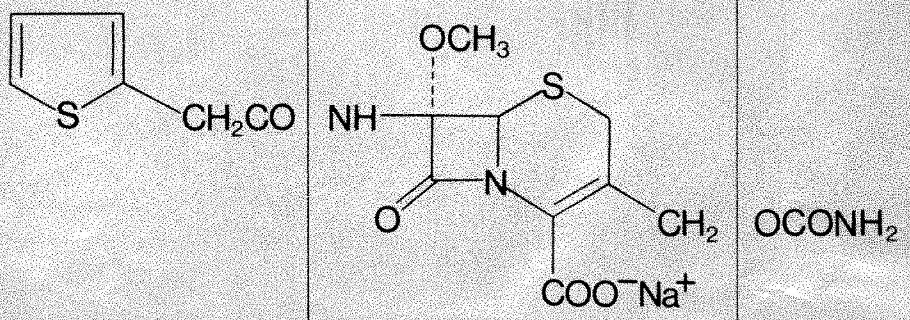

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Many Gram-negative pathogens are resistant to penicillins and cephalosporins through the action of the β-lactamases which are produced by these pathogens. 'Mefoxin' is remarkably stable in the presence of these bacterial β-lactamases, both penicillinases and cephalosporinases. Hence, the clinical efficacy of 'Mefoxin' extends to many infections caused by such pathogens.

'Mefoxin' is indicated for the treatment of the following infections caused by sensitive bacteria:
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'Mefoxin' is indicated for adjunctive therapy in the surgical treatment of infections including abscesses, infection complicating hollow visceral perforations, cutaneous infections, and infections of serous surfaces, whether caused by aerobes, mixed aerobes and anaerobes, or anaerobes.

Microbiology

'Mefoxin' is active *in vitro* against:

Aerobic bacteria

Gram-positive cocci including: *Staphylococci* (including coagulase-positive, coagulase-negative, and penicillinase-producing strains); Group A beta-haemolytic streptococci (*Streptococcus pyogenes*); Group B beta-haemolytic streptococci (*Streptococcus agalactiae*); *Streptococcus pneumoniae* (*Diplococcus pneumoniae*); other streptococci (except group D streptococci including enterococci, most strains of which are resistant, e.g. *Streptococcus faecalis*). *Gram-negative cocci including*: *Neisseria gonorrhoeae* (including penicillinase-producing strains); *Neisseria meningitidis*. *Gram-negative rods* (*facultative anaerobes*) *including*: *Escherichia coli*; *Klebsiella pneumoniae*; Klebsiella spp.; *Proteus mirabilis*; *Proteus* (indole positive); *Proteus vulgaris*; *Proteus rettgeri*; *Proteus morganii*; *Haemophilus influenzae*; *Serratia marcescens*; Providencia spp.; Salmonella and Shigella spp.

Anaerobic bacteria

Gram-positive cocci including: Peptococcus spp.; Peptostreptococcus spp.; Micro-aerophilic streptococcus. *Gram-positive rods including*: *Clostridium perfringens*; Clostridium spp.; Eubacterium spp.; *Propionibacterium acnes*. *Gram-negative cocci including*: Veillonella spp. *Gram-negative rods including*: *Bacteroides fragilis*; *Bacteroides melaninogenicus*; Bacteroides spp. (including both penicillin-susceptible and penicillin-resistant strains); Fusobacterium spp.

'Mefoxin' is active against some strains of the following bacteria: *Acinetobacter calcoaceticus* var *anitratum* (*Herellea vaginicola*); *Acinetobacter calcoaceticus* var *lwoffi* (*Mima polymorpha*); *Alcaligenes faecalis*; Citrobacter spp. and Flavo-bacterium spp.; Enterobacter spp.

'Mefoxin' is not active against Pseudomonas, most strains of enterococci and many strains of *Enterobacter cloacae*.

Dosage and administration

'Mefoxin' may be administered intravenously or intramuscularly. (See reconstitution directions for each route below.) Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organisms, and condition of the patient.

Therapy may be started while awaiting the results of susceptibility testing.

Dosage: The usual adult dosage is 1 g or 2 g of 'Mefoxin' every eight hours. (See chart.)

In adults with renal insufficiency, an initial loading dose of 1 g or 2 g may be given. After a loading dose, the following recommendations for *maintenance dosage* may be used as a guide.

Usual adult dosage

Type of infection	Dose	Frequency	Total daily dosage
Uncomplicated	1 g	Every 8 hours (occasionally every 6 hours)	3 g (4 g)
Moderately severe or severe	2 g	Every 8 hours (occasionally every 6 hours)	6 g (8 g)
Infections generally needing antibiotics in higher dosage	3 g (2 g)	Every 6 hours (Every 4 hours)	12 g

Maintenance dosage of 'Mefoxin' in adults with reduced renal function

Renal function	Creatinine clearance (ml/min)	Dose	Frequency
Mild impairment	50-30	1-2 g	Every 8-12 hours
Moderate impairment	29-10	1-2 g	Every 12-24 hours
Severe impairment	9-5	0.5-1 g	Every 12-24 hours
Essentially no function	<5	0.5-1 g	Every 24-48 hours

In the patients undergoing haemodialysis, the loading dose of 1 to 2 g should be given after each haemodialysis, and the maintenance dose should be given as indicated in the table above.

Intravenous administration: reconstitute 'Mefoxin' with Water for Injection BP. 1 g is soluble in 2 ml. Although 'Mefoxin' is very soluble, for intravenous use it is preferable to add 10 ml of Water for Injection BP to the 1 g vial or the 2 g vial. Shake to dissolve and then withdraw entire contents of vial into syringe.

For direct intravenous injection, 'Mefoxin' may be slowly injected into

Outstanding clinical benefits

Wide-ranging activity against Gram-negative and Gram-positive pathogens, anaerobes as well as aerobes.

Unusually high resistance to β-lactamase degradation.

Highly active against *Bacteroides fragilis* and strains of *E. coli*, Serratia, Klebsiella spp. and Proteus spp. (including indole positive strains) resistant to other antibacterial agents.

Offers high levels of active antibiotic in the body.

A record of relative safety comparable to the penicillins.

Prime indications include:

– Peritonitis, and other intra-abdominal and intrapelvic infections.
– Female genital tract infections
– Septicaemia
– Skin and soft tissue infections
– Bone and joint infections
– Urinary tract infections
– Respiratory tract infections (e.g. inhalation pneumonia)

Specific clinical profile

'Mefoxin' is exceptionally valuable wherever Gram-negative pathogens and anaerobes are involved in mixed infections. When mixed infections are suspected, therapy may be started while awaiting the results of susceptibility testing.

Mefoxin®

Cefoxitin sodium, MSD Injection

First of the cephamycins

the vein over a period of 3 to 5 minutes or may be given through the tubing when the patient is receiving parenteral solutions.

An intermittent intravenous infusion of 'Mefoxin' may be employed when large amounts of fluid are to be given. However, during infusion of the solution containing 'Mefoxin' it may be advisable temporarily to discontinue administration of any other infusion solution at the same site (by using an appropriate IV infusion set).

A solution of 'Mefoxin' may also be given by continuous intravenous infusion (see below for compatibility and stability).

Intramuscular administration ONLY
Reconstitute 'Mefoxin' 1 g with 2 ml of Water for Injection BP or 0.5% or 1% lignocaine hydrochloride (without adrenaline) solution. 'Mefoxin' is given by deep injection into a large muscle mass. Avoid injection into a blood vessel.

Compatibility and stability
A solution of 'Mefoxin' in Water for Injection BP may be added to the following solutions: 0.9% Sodium Chloride Injection BP, 5% or 10% Dextrose Injection BP, Dextrose and Sodium Chloride Injection (5% 0.9%, 5% 0.45%, or 4.3% 0.18%), Lactated Ringer's Injection USP, 5% Dextrose in Lactated Ringer's Injection, 5% or 10% invert sugar in water, 10% invert sugar in saline solution, 4.2% Sodium Bicarbonate Injection BP, M/6 Sodium Lactate Injection BP.

'Mefoxin', as constituted to 1 g/10 ml with Water for Injection BP, Water for Injection BP preserved with parabens or benzyl alcohol, 0.9% Sodium Chloride Injection BP or 5% Dextrose Injection BP, maintains satisfactory potency for 24 hours at room temperature, for 96 hours under refrigeration, and for 13 weeks in the frozen state.

'Mefoxin' can be administered concomitantly with such antibiotics as gentamicin, tobramycin, carbenicillin or amikacin. When 'Mefoxin' is administered with another antibiotic, they should not be mixed in the same syringe.

Contra-indications
'Mefoxin' is contra-indicated in persons who have shown hypersensitivity to cefoxitin. In the absence of clinical experience, 'Mefoxin' should not be administered to patients who have shown hypersensitivity to cephalosporins.

Precautions
There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and other β-lactam antibiotics: penicillins, and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most β-lactam antibiotics.

Before therapy with 'Mefoxin', careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibiotics. 'Mefoxin' should be given cautiously to penicillin-allergic patients.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. If an allergic reaction to 'Mefoxin' occurs, the drug should be discontinued.

The total daily dosage should be reduced when 'Mefoxin' is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see 'Dosage and administration'), because high and prolonged serum antibiotic concentrations can occur from usual doses.

Interference with laboratory tests
A false-positive reaction to glucose in the urine may occur with reducing substances but not with the use of specific glucose oxidase methods.

Use in pregnancy
Use of the drug in women of childbearing potential requires that the anticipated benefit be weighed against possible hazards. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the foetus due to 'Mefoxin'. There are no controlled studies with 'Mefoxin' in pregnant women.

Nursing mothers
'Mefoxin' is excreted in human milk.

Infants and children
Pending the outcome of clinical trials in progress, the conditions for use of 'Mefoxin' in infants and children remain to be defined.

Side effects
'Mefoxin' is generally well tolerated. Side effects rarely require stopping treatment and [illegible]

Local reactions
[illegible]

Allergic
[illegible]

Gastro-intestinal
[illegible]

Blood
[illegible]

Liver function
[illegible]

Kidney
[illegible] observed. The role of 'Mefoxin' [illegible] difficult to assess [illegible] or to impaired renal function [illegible]

Presentation
In vials containing 1 g or 2 g [illegible]

Product licence numbers [illegible]

Product authorisation [illegible]

Issued October [illegible]

Additional information is available [illegible] on request.

Basic NHS cost [illegible]

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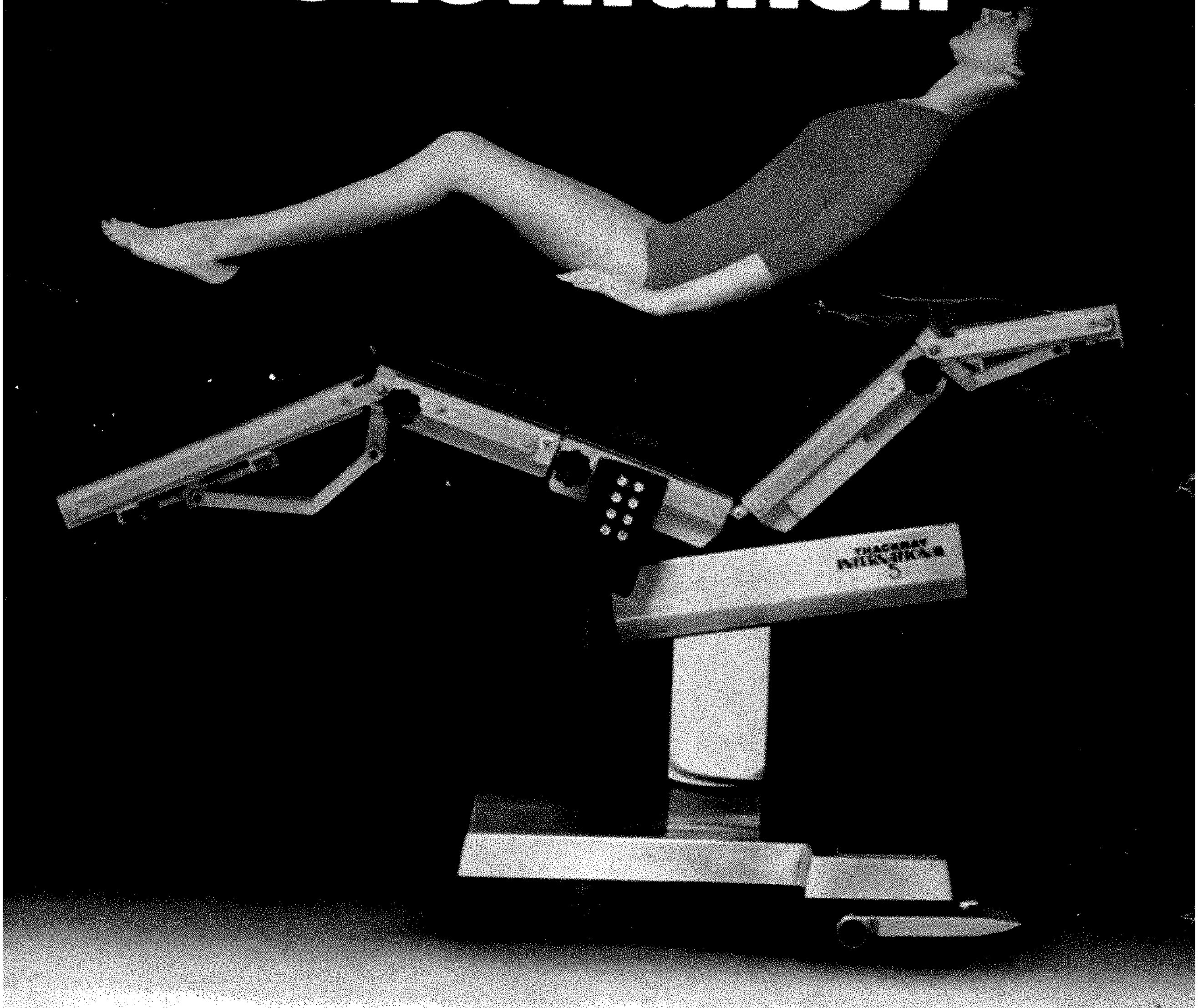

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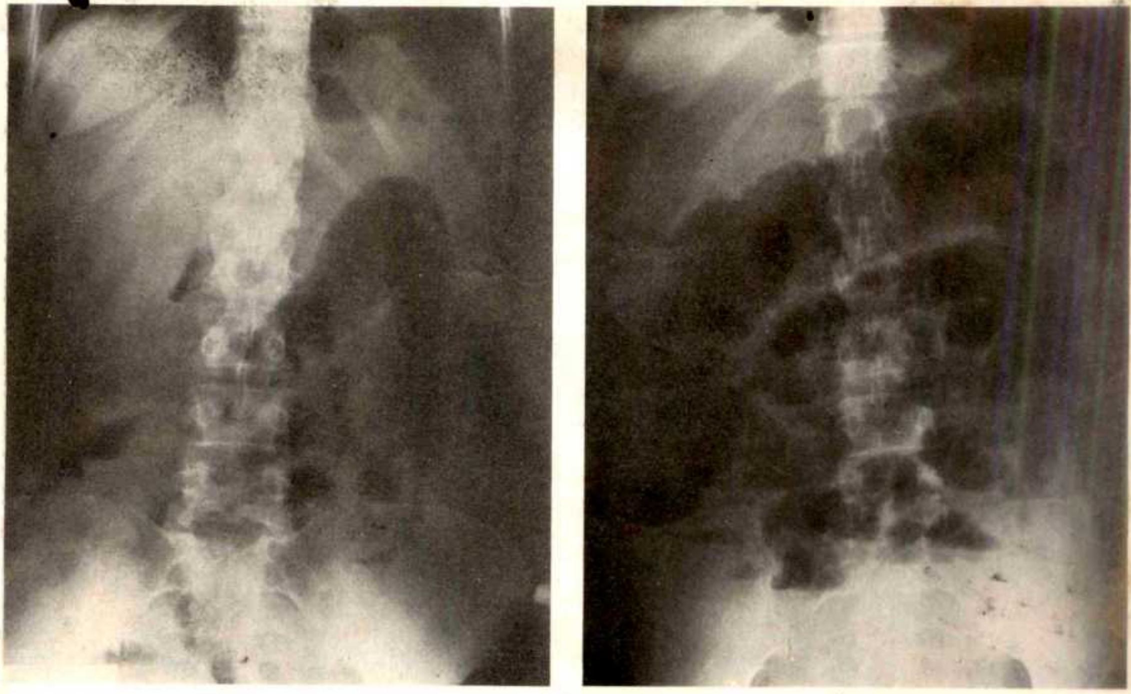
a b

Fig. 1. Plain X-rays of toxic dilatation of the colon in *Case* 6. *a*, Early changes with gas at the splenic flexure. *b*, The position 24 h later with total colonic and some small bowel distension.

Blood culture
It is customary in the infectious diseases unit to obtain routine blood cultures from all patients presenting with diarrhoea, as transient bacteraemia is a fairly common event in salmonella enterocolitis and a positive report may be forthcoming before the stool culture. This procedure was not helpful in the present cases.

Radiology
Abdominal radiographs in erect and supine positions showed gross dilatation of the colon (*Fig*. 1). There were no radiological differences between the inflammatory bowel disease and salmonella cases. Furthermore, in the resolving salmonella cases, barium enema examination sometimes demonstrated ulceration that was difficult to differentiate from ulcerative colitis or Crohn's disease of the colon, but repeat barium studies 3–6 months after the acute attack showed a return to a normal colonic outline.

Treatment and results
In patients with severe colitis, a period of intensive intravenous therapy was usually necessary to correct dehydration and restore the circulation. The cases were monitored very closely at this time by repeated pulse and blood pressure readings, abdominal girth measurement, abdominal X-rays and urea and electrolyte estimations.

During this period the salmonella cases tended to behave differently, with rapid progressive improvement in all aspects, even if there was toxic megacolon on X-ray. In the one salmonella case in which laparotomy was necessary, simple colostomy was carried out and the colon was spared because of different and more favourable appearances at operation. In the inflammatory bowel disease group of cases, progressive rapid improvement was not seen during the period of close observation. Several cases were stationary and several deteriorated in some aspects during this period and all 9 cases came to operation (*Table III*).

Table III. OPERATIVE FINDINGS AND TREATMENT

Case no.	Colon involved	Perforation	1st op.	2nd op.	Pathology
1	Total	Walled-off colon	SCI	AP	Crohn's
2	Total	No	SCI	AP	Crohn's
3	Total	No	SCI	—	Crohn's
4	Total	Walled-off ascending colon	SCI	IR	Crohn's
5	Total	No	SCI	AP	Crohn's
6	Total	No	SCI	—	CUC
7	Total	No	SCI	—	CUC
8	Total	Gangrene at splenic flexure, no perforation	SCI	AP	CUC
9	Total	No	SCI	AP	CUC
12	Right and transverse	Gangrene mid-transverse colon; no perforation	TC	CC	Salmonella

SCI, Subtotal colectomy and ileostomy; IR, ileorectal anastomosis; AP, abdominoperineal excision of rectum; CUC, chronic ulcerative colitis; TC, transverse colostomy; CC, close colostomy.

The mortality from persisting with medical treatment in toxic dilatation due to inflammatory bowel disease is so high that it was our policy to advocate operation as soon as this complication developed. The mortality of excisional surgery in this situation is less, and has been reported variously to be between 14 and 30 per cent (Goligher, 1975). Our surgical policy has been to use subtotal colectomy with ileostomy if there is no abscess formation, resorting to ileostomy and colostomy if there is a walled-off perforation (Turnbull et al., 1970). It was not considered necessary to use this latter procedure in any of the patients in this series, though in retrospect it might have been used in *Case* 1 who became severely ill with septicaemia after subtotal colectomy with ileostomy.

All the patients in the series are alive and well.

Discussion

It is usually stated in communications dealing with inflammatory bowel disease, either ulcerative colitis or Crohn's disease, that an infective cause should be excluded. We would certainly agree with this viewpoint, but our experience indicates that this can be very difficult (Mandal, 1974).

It should be accepted that many cases of acute diarrhoeal illness are caused by specific infections, among which salmonella infections are prominent. As a result, most clinicians would only admit cases of acute diarrhoeal illness into hospital under conditions of strict isolation.

It has been emphasized recently that salmonella infections may cause a severe colitis with profuse bloody diarrhoea showing sigmoidoscopic appearances and barium enema changes indistinguishable from inflammatory bowel disease (Mandal and Mani, 1976).

The present series goes further and demonstrates that toxic dilatation of the colon, accepted as one of the worst complications of inflammatory bowel disease, may also be caused by salmonella infection. The series showed that cases due to salmonella tended to resolve with medical treatment. On the other hand, the cases due to inflammatory bowel disease failed to improve rapidly with medical treatment but instead tended to deteriorate, so that surgical removal of the colon quickly became necessary.

In retrospect, the differentiation has been made to appear easy, but it was not so in the clinical situation at the time and it should be stressed that the decision to operate should be made entirely on the developing clinical picture and not solely on the presence or absence of a salmonella organism. Furthermore, the isolation of a salmonella organism in a case of acute colitis does not end the diagnostic difficulty because of the occasional occurrence of an associated salmonella infection in cases of inflammatory bowel disease. This is indeed a doctor's dilemma, both from a diagnostic and therapeutic viewpoint.

It is concluded from this series that salmonella infection needs to be considered in the differential diagnosis throughout the entire spectrum of severity of acute colitis, including cases of toxic dilatation.

In the assessment and management of these cases, our experience has convinced us of the value of a team with medical and surgical facilities and with experience of the whole range of infective and non-infective inflammatory bowel disease.

References

APPELBAUM P. C., SCRAGG J. and SCHONLAND M. M. (1976) Colonic involvement in salmonellosis. *Lancet* **2**, 102.

BOYD J. F. (1976) Colonic involvement in salmonellosis. *Lancet* **1**, 1415.

BROOKE B. N. and SAMPSON P. A. (1964) An indication for surgery in acute ulcerative colitis. *Lancet* **2**, 1272–1273.

DAY D., MANDAL B. K. and MORSON B. M. (1978) *Histopathology* **2**, 117-131.

GOLIGHER J. C. (1975) *Surgery of the Anus, Rectum and Colon*, 3rd ed. London, Baillière, Tindall.

MANDAL B. K. (1974) Colonic involvement in salmonellosis. *Br. Med. J.* **1**, 326.

MANDAL B. K. and MANI V. (1976) Colonic involvement in salmonellosis. *Lancet* **1**, 887–888.

MARSHAK R. H., LESTER L. J. and FRIEDMAN A. I. (1950) Megacolon, a complication of ulcerative colitis. *Gastroenterology* **16**, 768–772.

RADSEL-MEDVESCEK A., ZARGI R., ACKO M. et al. (1977) Colonic involvement in salmonellosis. *Lancet* **1**, 601.

TURNBULL R. B., WEAKLEY F. L., HAWK W. et al. (1970) Choice of operation for the toxic megacolon phase of non-specific ulcerative colitis. *Surg. Clin. North Am.* **50**, 1151–1169.

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A clinical trial of endolymphatic therapy in malignant melanoma: interim report of the progress of the Medical Research Council trial

MRC WORKING PARTY ON ENDOLYMPHATIC THERAPY IN MALIGNANT MELANOMA*

SUMMARY

This report presents the interim results of the MRC trial on the treatment of Stage I melanoma of the lower limb by endolymphatic therapy.

Over a 10-year period a group of 146 patients has been entered into the trial. Although total recurrence rates were not significantly affected by endolymphatic therapy, recurrence in the lymph nodes was largely prevented. More patients in the standard treatment group needed the more major procedure of block dissection.

The survival rates for the endolymphatic and standard treatment groups did not differ significantly.

THE encouraging clinical results in the treatment of melanoma by the use of endolymphatic therapy (Jantet, 1958, 1962; Jantet et al., 1964) stimulated interest in this technique. The method was similar to that used in diagnostic lymphography except that a radioactive isotope was bound to the diagnostic agent to irradiate regional lymph nodes involved with tumour. Animal studies also showed definite advantages for endolymphatic therapy compared with controls (Edwards, 1966; Edwards et al., 1966).

A controlled clinical trial was subsequently sponsored by the Medical Research Council in 1966. This trial was designed to compare two methods of management in patients with stage 1 melanoma of the lower limb, either by excision of the primary tumour followed by endolymphatic therapy to the regional nodes or by excision of the primary tumour followed by other treatment, not involving endolymphatic therapy, such as immediate or delayed block dissection according to the discretion of the clinician responsible.

Patients and methods

Patients aged between 15 and 70 years with a clinical diagnosis of malignant melanoma of the lower limb were eligible for admission to the trial, except those patients: (*a*) with clinical involvement of the regional lymph nodes; (*b*) with signs of distant spread on general clinical examination or on a chest radiograph; (*c*) with widely scattered satellite lesions on the same limb as the primary lesion which could not be removed by surgery at the same time as the primary lesion; (*d*) who were found to be pregnant; (*e*) who were referred specifically for endolymphatic therapy.

Allocation to the two treatment groups

The main centres involved in the trial were St Thomas' Hospital, London, the University Hospital of Wales, Cardiff, Mount Vernon Hospital, Northwood, the Postgraduate Medical School, Hammersmith, and the Royal Infirmary, Glasgow. Patients were entered into the trial from these centres having met the conditions of entry, including histological confirmation of the diagnosis of invasive malignant melanoma by the local pathologist. Patients were randomly allocated to either 'endolymphatic therapy' or 'therapy by existing methods' using the sealed-envelope technique (randomization being separate for each centre).

Subsequently, the local pathologist would send one stained and one unstained section of the primary melanoma to each of the pathologists comprising the melanoma reference panel. All three members of the panel had to agree that the sections showed invasive malignant melanoma. If the diagnosis was not accepted the patient was excluded from the trial. (The members of this panel were Dr O. C. Lloyd, Professor S. J. de Navasquez and Dr I. W. Whimster. Professor N. F. C. Gowing joined the panel later in place of Professor Navasquez.)

After random allocations detailed clinical information regarding each patient was recorded (analysis of which will be presented at a later date).

Treatment

Standard treatment: Treatment in the 'existing methods', standard or non-endolymphatic therapy group consisted of various schemes of management. Some surgeons followed excision of the primary lesion by block dissection of regional nodes in all cases. Others awaited clinical evidence of involvement before performing dissection. The essential difference was that in this group endolymphatic therapy was not used.

Technique of lymphography: It was decided that no centre should enter the trial until experience in the relevant technique had been gained by the appropriate clinician. The suggested technique for endolymphatic therapy was agreed by the Working Party and circulated to all centres involved in the trial. This technique was developed at St Thomas' Hospital (Edwards and Kinmonth, 1968; Edwards, 1969).
The first isotope combination used in the trial was ^{131}I-lipiodol. Subsequently it was found that ^{32}P-lipiodol was probably more

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* Present membership: *Chairman* J. B. Kinmonth, Professor of Surgery, St Thomas' Hospital Medical School, London; *Secretary* J. M. Edwards, Senior Lecturer, St Thomas' Hospital Medical School, London; *Members* D. L. Crosby, Consultant Surgeon, University Hospital of Wales, Cardiff; G. E. Flatman, Deputy Director, Institute of Radiotherapeutics, Glasgow; A. P. M. Forrest, Professor of Surgery, University of Edinburgh; T. Gibson, Professor of Bioengineering, Canniesburn Hospital, Glasgow; N. F. C. Gowing, Professor of Pathology, Royal Marsden Hospital, London; A. L. Johnson, Statistician, MRC Statistical Research and Services Unit, London; O. C. Lloyd, Reader in Morbid Anatomy, University Medical School, Bristol; J. S. Macdonald, Consultant Radiologist, Royal Marsden Hospital, London; G. W. Taylor, Professor of Surgery, St Bartholomew's Hospital, London; N. Thompson, Consultant Plastic Surgeon, Mount Vernon Hospital, Northwood; I. W. Whimster, Reader in Pathology of Skin Diseases, St Thomas' Hospital Medical School, London.
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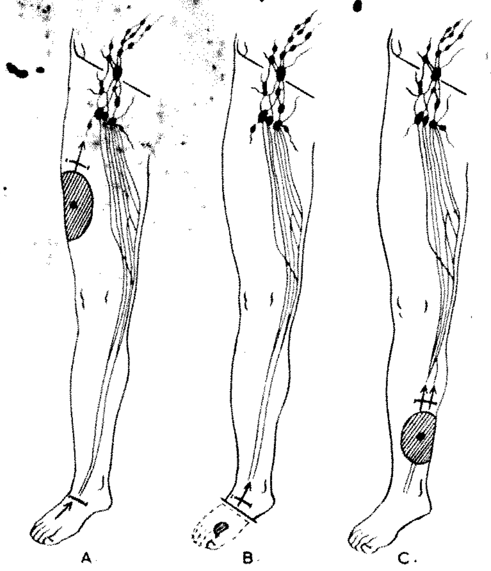

Fig. 1. Melanoma of the lower imb: primary growth shaded and site of injection of radioactive material indicated by arrows.

effective and this was used from 1968. The clinical advantages of ^{32}P-lipiodol as compared with ^{131}I-lipiodol may be summarized as follows:

1. Increased maximum penetration of β-particles of 8 mm as compared with 2 mm for ^{131}I.

2. Pure β-emitter, reducing any radiation hazard to personnel in theatre.

3. Increased half-life of 14 days as compared with 8 days for radio-iodine.

Owing to faster metabolic turnover of lipiodol in the lungs as opposed to the lymph nodes there would be potentially less β-radiation dosage to the lungs with ^{32}P than with the use of radio-iodine.

With ^{131}I-lipiodol the aim was to achieve a dose of 35 mCi at the time of the injection and with ^{32}P, a dose of 6 mCi. This dosage was calculated on the basis of experimental and clinical studies evaluating the histological effects of varying dosages. The dose was decided on the basis of the observation that destruction of lymph nodes with small metastases occurred with regularity. The actual β-dose in rads was estimated by using the β-emitter dosimetry formula (Hine and Brownell, 1956).

By direct measurement of radioactivity on excised nodes, and by confirming the uniform distribution of the isotope by the histological effect and autoradiography, the use of this formula has shown the β-dose to reach 100 000 rad with the dosage quoted for clinical use (Edwards and Kinmonth, 1967).

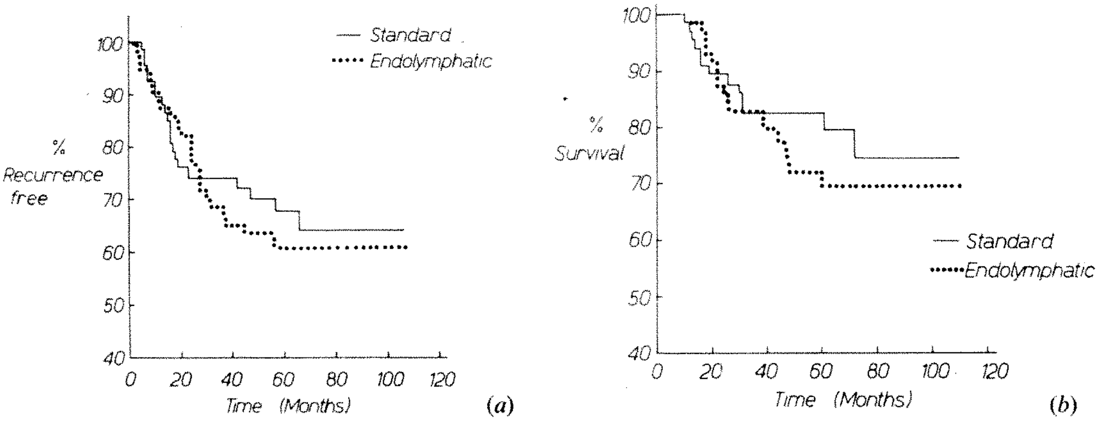

Fig. 2. *a*, Actuarial percentage recurrence-free curves for standard treatment ($n = 72$) and endolymphatic treatment ($n = 74$). *b*, Actuarial percentage survival curves for standard ($n = 72$) and endolymphatic ($n = 74$) treatment.

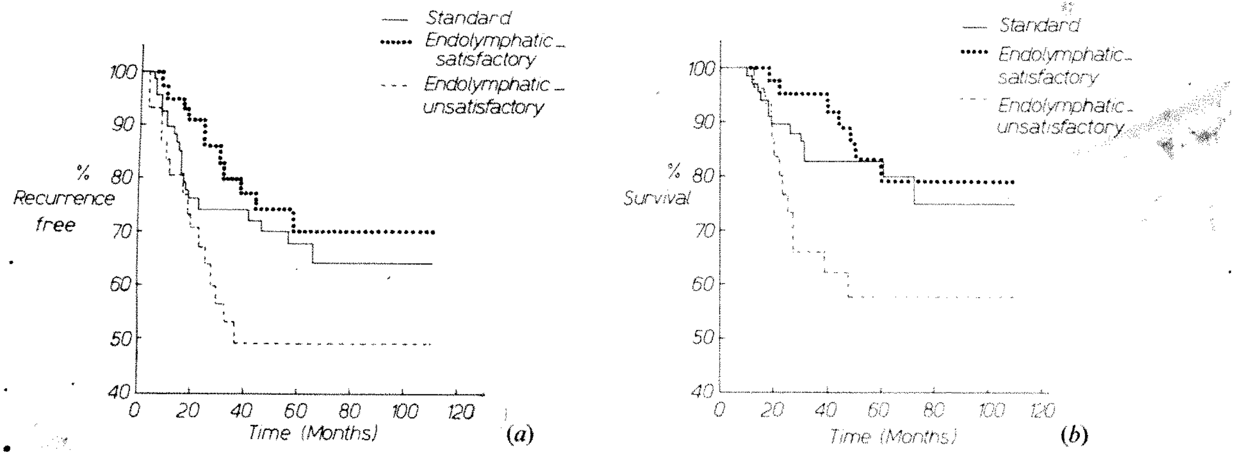

Fig. 3. *a*, Actuarial percentage recurrence-free curves for standard treatment ($n = 72$) and for 'satisfactory' ($n = 42$) and 'unsatisfactory' ($n = 32$) endolymphatic treatment. *b*, Actuarial percentage survival curves for standard treatment and 'satisfactory' and 'unsatisfactory' endolymphatic treatment (numbers in each group as for *a*).

The following factors were regarded as particularly important:

1. Wherever possible, the injection was proximal to the site of the primary lesion (*Fig.* 1).

2. For growths in the thigh, anterior leg and foot a lymphatic on the dorsum of the foot was injected, provided that the primary melanoma site did not lie across the pathway of the lymphatics. A 10 per cent aqueous and autoclaved solution of Patent Blue was injected between the toes to demonstrate the lymphatics and also around the melanoma site in those cases in which multiple injections were necessary.

3. For growths on the back of the leg (in the drainage area of the small saphenous vein) where lymph might drain via the popliteal fossa, an attempt was made to inject a lymph trunk proximal to the primary site. If this was unsuccessful the usual dorsal pedal injection was made.

4. Lugol's iodine was given orally 3 days before the injection of radio-iodine.

5. Cannulation of the lymphatic was made with a no. 30 needle, swaged on to polyvinyl tubing (Rutt et al., 1964) that was connected to a syringe containing the radioactive material.

6. The injection was made slowly, taking no less than 10 min for each millilitre, to avoid extravasation of the radioactive material through the walls of the lymphatic.

7. Screening and protection. The sterile syringe, with a measured amount of radioactive lipiodol, was brought to the theatre in a lead container and transferred and carefully connected to the lymphangiogram set in the autoinjector, surrounded by 2·0 cm of lead. The remaining lipiodol in the syringe and tubing was measured so that the total dose injected was known.

8. Radiographs were taken early in the course of the injection and the initial cases were also monitored with a modified Geiger counter.

Post-injection treatment: Radiographs of the limb, pelvis and lumbar regions were taken at the end of the injection and 24 and 48 h later to show if any extravasation had occurred and to demonstrate the state of the regional nodes. Radiographs of the pelvic areas were taken in three projections, antero-posterior, lateral and oblique. If the nodes showed filling defects suggesting tumour deposits, then surgical extirpation of these nodes was required. The patients remained in the study, however, in the endolymphatic therapy group.

A total body scan was done 48 h after injection. All urine was saved for 5 days and the radioactivity assayed daily; blood samples were also taken for assay.

White cell blood counts were made at 5 days and 21 days after injection.

At subsequent reviews, white cell counts and radiographs of the pelvis and abdomen were taken and correlated with the clinical assessment of the lymph nodes. The surgeon has to decide whether to excise lymph nodes should metastases of significant size show on lymphadenograms. It was suggested that an interval of at least 4 weeks should elapse before excision to allow the radioactivity to subside to a safe level. In view of the longer half-life of ^{32}P, a longer period of about 6 weeks was suggested before block dissection.

Follow-up

Patients were seen monthly for the first 3 months, then every 3 months for 2 years and thereafter 6-monthly. Questionnaires were completed on each occasion which recorded details of any complications, such as lymphoedema or local skin reactions, or progress of the disease, such as enlargement of nodes needing block dissection. Note was also made of subsequent pregnancy or the onset of the menopause, the occurrence of other forms of malignant disease and the period spent in hospital or away from work. A chest radiograph was taken 1 year after treatment.

If a patient declined later treatment, block dissection for instance, he was kept in the trial and counted as a failure of treatment, a special note being made of the refusal to enable these cases to be withdrawn if necessary from the final assessment of the trial. A failed attempt at endolymphatic therapy was also counted as a failure of initial treatment, the patient being kept in the trial and a note made.

A second treatment by endolymphatic therapy was given if considered necessary. In both groups of patients the addition of general or local treatment was not contraindicated if there was recurrence. The surgeon or radiotherapist was allowed to treat any subsequent recurrence in the way he thought best.

Results

Entry to the trial was terminated on 30 November 1974, and by then 171 patients had been entered (*Table I*). This report has been compiled from information received on the state of the patients to 1 March 1975. In 16 patients (9·4 per cent of the total entered) the diagnosis of malignant melanoma was not confirmed histologically, and these patients were withdrawn from the trial. A further 9 patients (5·3 per cent of the total entered) were withdrawn for other reasons, i.e. stage 2 melanoma (1 patient), presence of secondaries (2 patients), presence of second primary melanoma (1 patient), disagreement amongst the pathology panel (3 patients), failure to give the allocated treatment (1 patient) and incorrect entry of a referral for endolymphatic therapy (1 patient). Thus, of 171 patients entered into the trial, 146 (85·4 per cent) were eligible for inclusion, and the analyses reported here are based on information received about them (*Table I*). Seventy-two patients (49·3 per cent of those eligible for inclusion) received standard therapy, 74 (50·7 per cent) received endolymphatic therapy.

In 135 patients (68 standard therapy, 67 endolymphatic therapy) treatment of the primary lesion was by wide excision and skin grafting. The average area excised was 36 cm^2. The deep fascia was left intact in 95 patients (48 standard, 47 endolymphatic) and the skin graft taken from the contralateral limb. Nine patients (3 standard, 6 endolymphatic) were treated by amputation, usually when the melanoma occurred in the subungual site (and the digit was amputated). For 2 patients (1 standard, 1 endolymphatic) the treatment of the primary lesion was not recorded.

There were no important differences between the standard therapy group and the endolymphatic group as regards age and sex distribution, the history, description and area of the primary lesion, the presence of satellite lesions, previous treatment and the occurrence of pain, pruritus and significant trauma.

The actuarial percentage recurrence-free and survival rates at yearly intervals from 1 to 5 years are shown for standard and endolymphatic therapies in *Table I*; the corresponding survival curves are shown in *Fig.* 2. Comparison of the recurrence-free and survival curves for the two therapies, using the log rank test, indicates no significant difference between them ($P = 0·67$ and $P = 0·43$ respectively).

Soon after the start of the trial, a significant failure rate in the application of endolymphatic therapy was apparent. This was stated quite simply as 'not satisfactorily administered' in the record form, owing to failure to identify lymphatics or to cannulate them even when identified. The high failure rate was also reflected in the measurements and radiographic studies; the dose administered was low, and on radiographs, the lymph nodes were not satisfactorily opacified. Some patients were given endolymphatic therapy a long time after treatment of the primary (in some cases there was over a year's delay). On further inquiry, it seemed that these were stage 2 melanomas having treatment for lymph nodes obviously involved with tumour. After consideration, it was decided that

Table I: ACTUARIAL PERCENTAGES OF PATIENTS RECURRENCE-FREE AND SURVIVING AT YEARLY INTERVALS UP TO 5 YEARS FROM ENTRY TO THE TRIAL ACCORDING TO THERAPY

		Withdrawn for			Actuarial percentage									
					Recurrence-free at (yr)					Surviving at (yr)				
Treatment group	Total entered	Negative or equivocal histology	Other reasons*	Total eligible	1	2	3	4	5	1	2	3	4	5
Standard	83	6	5	72	89·6	74·2	74·2	70·1	67·7	97·0	89·3	82·3	82·3	82·3
Endolymphatic: satisfactory	—	—	—	42	95·2	85·4	80·0	74·1	70·2	100·0	95·2	95·2	83·0	78·8
Endolymphatic: unsatisfactory	—	—	—	32	80·4	63·3	49·0	49·0	49·0	96·7	76·4	66·0	57·3	57·3
Endolymphatic: total	88	10	4	74	89·0	76·2	65·1	63·3	61·1	98·6	87·3	82·9	72·1	69 7

* Includes 1 stage 2 melanoma, 2 patients with secondaries, 3 patients regarding whom the pathological panel disagreed on diagnosis, 1 patient with a second primary melanoma, 1 patient given the 'wrong' treatment and 1 patient referred for endolymphatic therapy incorrectly entered in the trial.

Table II: SITE OF PRESENTATION OF INITIAL RECURRENCE

Group	No. of patients	Recurrence in nodes	%	Recurrence in skin*	%
Standard methods	69	13	19	4	6
Endolymphatic: satisfactory	48	1	2	7	16
Endolymphatic: unsatisfactory	25	3	12	8	32

* Recurrence in skin includes the primary site and distal areas.

the endolymphatic therapy group be subdivided to isolate those patients whose treatment was unsatisfactory.

The administration of endolymphatic therapy was regarded as unsatisfactory for any of the following reasons:

1. Stated as not satisfactorily administered on record form (9 patients).
2. Dosage too low (less than 4 mCi ^{32}P or less than 25 mCi ^{131}I) (3 patients).
3. The interval between surgery and endolymphatic therapy exceeded 3 months (13 patients).
4. The paravertebral lymph nodes were not filled (12 patients).

Five patients included under group 1 also fall into another of the groups 2 to 4.

Thus, 32 patients (43·2 per cent of those receiving endolymphatic therapy) were considered to have been treated unsatisfactorily. In the remaining 42 patients, the endolymphatic therapy was considered satisfactory. The actuarial recurrence-free and survival rates for these two groups are also shown in *Table I*. The corresponding curves are shown in *Figs*. 3*a* and *b* respectively, together with the curve for the standard therapy group. The recurrence-free and survival rates are significantly higher in the 'satisfactory' group than in the 'unsatisfactory' group (log rank test, $P = 0{\cdot}024$ and $P = 0{\cdot}014$ respectively). Similarly, both the recurrence-free and survival rates are higher in the standard therapy group than in the 'unsatisfactory' group, though only the latter is statistically significant at $P = 0{\cdot}05$ (log rank test, $P = 0{\cdot}091$ and $P = 0{\cdot}047$ respectively). There are no significant differences between the standard therapy group and the 'satisfactory' group.

The presentation of initial recurrence is of particular interest and is shown in *Table II*, for recurrences before March 1974. There appears to be a different pattern in the mode of recurrence in the different treatment groups; in the endolymphatic group the initial recurrence tends to be in the skin rather than in the lymph nodes whereas in the standard therapy group lymph node recurrence is high.

Discussion

In view of the enthusiasm of the participants at the onset of the trial, it has been disappointing that only a relatively small number of patients are available for analysis, even though the trial was continued for almost 10 years. Some points of interest have, however, emerged.

1. When treated adequately by meticulous attention to the primary lesion, melanoma of the lower limbs is not nearly as serious a disease as has been previously described. Standard treatment methods give a 5-year actuarial recurrence-free rate of 67 per cent when treatment is applied to stage 1 melanoma.
2. Endolymphatic therapy significantly reduced the recurrence rate in the lymphatic system, although skin recurrence was higher in this group. The interpretation of this trend may indicate that prevention of lymphatic relapse seems to have allowed relapses elsewhere to be seen first, but without appreciably reducing the total relapse rate. Probably a more likely explanation is that destruction of small metastases in nodes was effected by endolymphatic therapy at the price of a lymphatic blockage effect causing in-transit metastases to develop in the skin. Mild lymphatic oedema is occasionally seen after endolymphatic therapy.
3. The major factor that could influence the results in all the groups is the pathology of the primary tumour. All lesions have been broadly classified as *invasive malignant melanoma*, but this classification is now recognized as too wide. The clinician can recognize certain macroscopic pathological types that can be regarded particularly with foreboding, and further work by the pathologist must aim at determining the characteristics of these 'bad' lesions. We would conclude that a further, more detailed, pathology survey is indicated and these results will be presented in the final analysis of the trial.
4. A number of patients in the standard treatment group required regional node dissection as part of

this treatment, either initially or subsequently. This is a more major procedure for the patient than an endolymphatic injection. On the other hand, endolymphatic injection requires specialized skill which may not be readily available in all centres.

References

EDWARDS J. M. (1966) Therapeutic aspects of lymphography. MS thesis, University of London.

EDWARDS J. M. (1969) Malignant melanoma. Treatment by endolymphatic radio-isotope infusion. *Ann. R. Coll. Surg. Engl.* **44**, 237–254.

EDWARDS J. M., GIMLETTE T. M., CLAPHAM W. F. et al. (1966) Endolymphatic therapy of tumours with particular reference to the VX2 tumour in *Lepus cuniculus*. *Br. J. Surg.* **53**, 969–978.

EDWARDS J. M. and KINMONTH J. B. (1967) Radio-isotopes in lymph node tumours. In: *Progress in Lymphology*. Stuttgart, Thieme Verlag, p. 243.

EDWARDS J. M. and KINMONTH J. B. (1968) Endolymphatic therapy for malignant melanoma. *Br. Med. J.* **1**, 18–22.

HINE G. J. and BROWNELL G. L. (1956) *Radiation Dosimetry*. New York, Academic Press.

JANTET G. H. (1958) Communication to the Ninth Scientific Meeting of the Surgical Research Society, London.

JANTET G. H. (1962) Direct intralymphatic injections of radioactive colloidal gold in the treatment of malignant disease. *Br. J. Radiol.* **35**, 692–697.

JANTET G. H., EDWARDS J. M., GOUGH M. H. et al. (1964) Endolymphatic therapy with radioactive gold for malignant melanoma. *Br. Med. J.* **2**, 904–906.

RUTT D. L., GOUGH M. H. and KINMONTH J. B. (1964) Disposable lymphangiography set. *Lancet* **1**, 475–476.

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Royal College of Surgeons of England

The first joint meeting of the Royal College of Surgeons of England and the American College of Surgeons is to take place at the Queen Elizabeth Hall in London from 12 to 14 March 1979. The English College is responsible for the detailed planning of the meeting which is expected to attract at least 500 American surgeons, and the meeting is of course of special interest to their colleagues in England.

'The Generality of Surgery' is the theme of the meeting and this has been chosen to illustrate the conviction that, notwithstanding the development of specialties, there is a large area of common ground shared by most surgeons at some time in their professional life. In planning the programme, therefore, almost all the time has been allotted to plenary sessions in the hope that surgeons working on many different specialties and subspecialties can be brought together in a way that the advent of specialist societies with their own meetings has made increasingly rare. The particular interests of dental surgeons and anaesthetists are included in the symposium on 'Trauma and Intensive Care'. Other symposia are entitled 'The Growing Edge of Surgery' (with sections on Endoscopy, Modern Trends in Diagnostic Imaging and Implants), 'Early Carcinoma of the Breast', 'Abdominal Cancer—is major therapy worthwhile?', 'Trauma and Intensive Care', 'Parathyroid Disease' and 'Wound Healing and Suture Materials'. Each symposium has a British convener and at least one major American contributor. The meeting will conclude with addresses delivered by Dr William H. Muller jun., Chairman of the Board of Regents of the American College of Surgeons, and by Lord Smith, Past President of the Royal College of Surgeons of England.

A programme for ladies and other family members, a social programme and a trade exhibition have also been arranged.

Surgical and Faculty Fellows of the Royal College of Surgeons of England are invited to apply for further particulars to:

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R. S. JOHNSON-GILBERT, OBE, MA
Secretary
Royal College of Surgeons of England

Br. J. Surg. Vol. 66

An abdominal extraperitoneal approach for the difficult orchidopexy

PETER F. JONES AND FREDERICK H. BAGLEY*

SUMMARY

An abdominal extraperitoneal approach is described for use in patients who have a severe degree of incomplete descent of the testicle. In 86 such operations, the testicle was placed in the scrotum in 85. The approach allows certainty of diagnosis in cases of anorchia and it is helpful when orchidopexy has to be combined with a herniotomy in infancy.

THE operation of orchidopexy has changed very little since the first detailed description of Arthur Dean Bevan of Chicago in 1899. An operation which has remained in general use for so long must be effective, but there are, nevertheless, a number of patients in whom successful orchidopexy is not achieved by this technique in one operation. Bevan himself recognized this when he wrote in 1903:

> I have found by experience that in operating on cases in which the testicles are not palpable I could not, by the method described, free the testicle sufficiently to bring it into the scrotal pocket without tension. The tense structures which prevented reduction were the spermatic vessels not the vas.

Most surgeons would agree that it is the freeing of the testicular vessels which is the crucial part of the operation, and in operating on impalpable testicles it is essential to do this retroperitoneally, above the deep inguinal ring. To achieve this, attention has generally been focused on enlarging the deep inguinal ring. Davison (1911) advised division of the posterior wall of the inguinal canal and Gross (1953) advocated dividing the conjoint tendon laterally and the inferior epigastric vessels medially to improve the access to the retroperitoneal space and to straighten the line of the testicular vessels (*see* legend to *Fig.* 7). Using these manoeuvres, surgeons have achieved surprisingly different results. Bevan (1929), after 30 years of experience, failed to place the testicle in the scrotum in only 3–4 per cent of his patients; the failure rate of others has varied from 1·3 per cent (Gross and Replogle, 1963) and 3 per cent (Persky and Albert, 1971) up to 21 per cent (Firor, 1971) and 40 per cent (Dougall et al., 1974).

These figures suggest that the procedure still presents an appreciable problem, even if the deep inguinal ring is opened widely, and it is well known that the exploration for an abdominal testicle through this approach can be very taxing. In these difficult cases we believe that a better approach is to expose the deep inguinal ring from above, through an abdominal incision that will also allow an extensive retroperitoneal dissection.

The extraperitoneal approach was suggested for inguinal hernia repair by Cheatle in 1921, and 3 years later Paul La Roque of Richmond, Virginia, suggested an abdominal transperitoneal approach for orchidopexy. It was not until 1957 that Florence drew attention to the excellent exposure of the testicular vessels which he had obtained whilst carrying out an extraperitoneal dissection of the lower end of the ureter through a lower midline incision: later he deliberately explored 7 maldescended testicles in this way. Since then others (Bourque, 1961; Lipton, 1961; Jacobson, 1966) have reported enthusiastically on orchidopexy performed through a lower midline or Pfannenstiel incision, with extraperitoneal dissection.

Over the past 4 years we have become convinced of the value of an abdominal extraperitoneal approach for orchidopexy but we have used a muscle-splitting incision (Fowler, 1900; Weir, 1900).

Technique

1. Because the operation uses an abdominal incision it is helpful if the anaesthetist provides adequate muscular relaxation.

2. The skin incision is placed appreciably higher than usual and runs medially in a skin crease from a point internal to the anterior superior iliac spine to a point just short of the midline (*Fig.* 1). External oblique is split in the line of its fibres to reveal the linea semilunaris. This is picked up and incised horizontally with a knife, the anterior rectus sheath being split medially with scissors. Laterally, the muscular bellies of internal oblique and transversus abdominis are also split with the help of scissors and then the two index fingers are inserted through all layers and the muscle-split completed (*Fig.* 2).

3. Retractors are inserted and the transversalis fascia opened to reveal the surface of the peritoneum. If the lower retractor is now lifted the processus vaginalis will be seen entering the deep inguinal ring, and often the testicle is seen at this level, lying within the processus vaginalis (*Fig.* 3).

4. The processus vaginalis is picked up, gently separated from the deep ring and rotated slightly. This reveals the testicular vessels and the vas deferens adhering to the posterior aspect of the processus: these structures can be gently separated from the processus by sharp and blunt dissection. When this process is complete, the processus (i.e. the neck of the inguinal hernial sac) should be divided and tied off flush with the peritoneal cavity, the ligature being held long (*Fig.* 4).

5. Gentle traction on the testicular vessels and the vas then delivers the testicle from the inguinal canal: the testicle is usually tethered at its lower pole by connective tissue strands, and these are divided. Once freed, the testicle is brought out of the wound and the retroperitoneal dissection is commenced by pulling upwards and forwards on the ligature on the hernial neck; this reveals the retroperitoneal space, which can be further opened up by retraction (*Fig.* 4). The testicular artery and veins are freed by progressive division of the restraining strands of 'lateral spermatic fascia'. This freeing-up process can be carried towards and sometimes up to the lower pole of the kidney. A similar freeing of the vas deferens is carried medially, down into the pelvis. Following this extensive dissection the spermatic cord has usually lengthened sufficiently to allow the testicle to be placed at the level of the mid-scrotum (*Fig.* 5). If this is so, the retroperitoneal dissection is complete and the next step is described in paragraph 8.

6. Sometimes the processus vaginalis is seen entering the deep ring but there is no sign of the testicular vessels or vas. The testicle may then be found adherent to the posterior surface of the peritoneum 1–2 cm or more above the deep ring. If the neck of the hernial sac is divided and opened up this allows the

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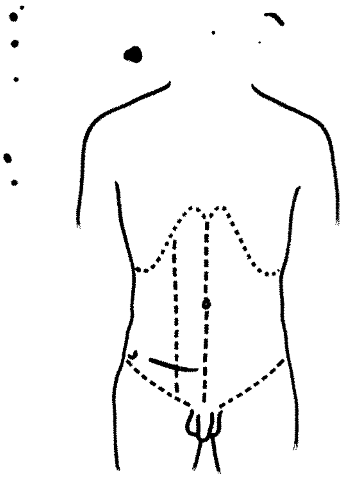

Fig. 1. The line of incision.

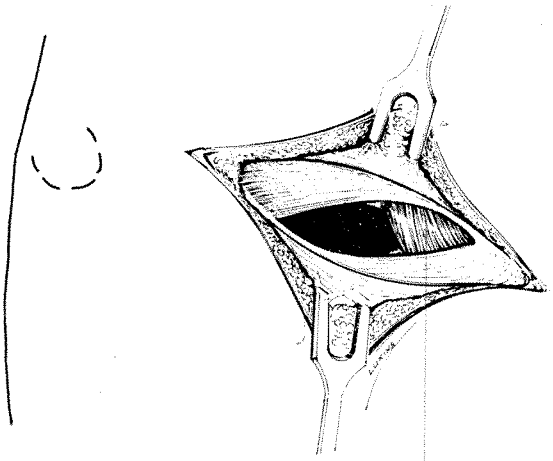

Fig. 2. The incision is held open to show the two layers of muscle which are split: first, external oblique and secondly, the internal oblique/transversus layer. The incision into the anterior rectus sheath reveals the lateral edge of rectus abdominis. (In *Figs.* 2–6 the patient is viewed as if from the foot of the operating table. The position of the right anterior superior iliac spine is shown as a dotted semicircle.)

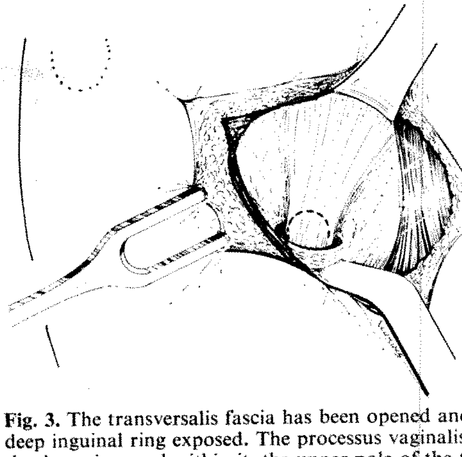

Fig. 3. The transversalis fascia has been opened and the deep inguinal ring exposed. The processus vaginalis enters the deep ring, and within it, the upper pole of the testicle can be seen (dotted line).

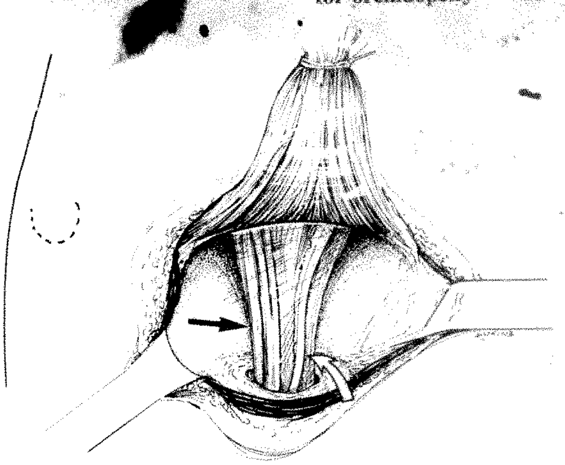

Fig. 4. The inguinal hernial sac has been dissected off the testicular vessels (black arrow) and the vas (white arrow), and a ligature has been placed around its neck. Traction on the neck of the sac opens up the retroperitoneal space and allows freeing of the vessels and vas to commence.

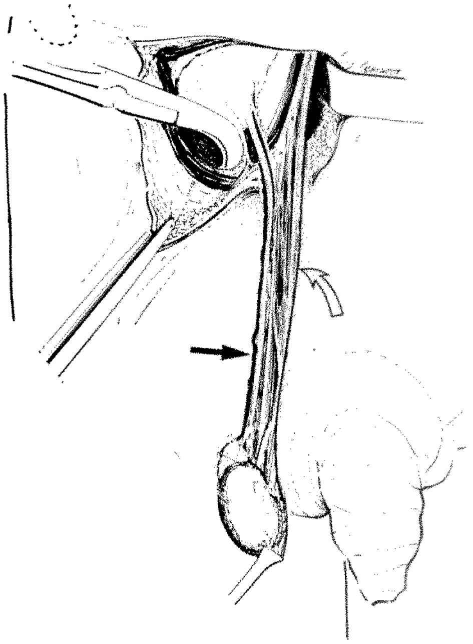

Fig. 5. Gentle traction on the testicle shows that sufficient retroperitoneal mobilization of the vessels and vas has been achieved. The Moynihan forceps has been passed into the empty deep inguinal ring.

testicle to be detached from the surrounding peritoneum and the gap so made in the peritoneum can be closed with a running suture of fine polypropylene. The testicle can then be drawn down and the testicular vessels and the vas freed in the manner already described. By this method we have found it possible to bring an abdominal testicle down into the scrotum at the one operation on six occasions.

7. The excellent exposure obtainable through this incision is also of great value in cases of anorchia. When the deep ring is examined from above and neither vessels nor vas are found to enter it, these two structures are sought in the retroperitoneal space. On two occasions we have found the vas at the pelvic

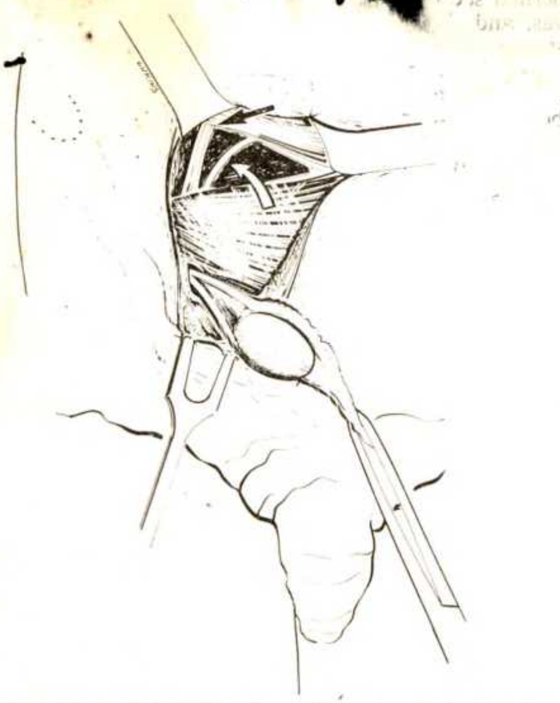

Fig. 6. The testicle has been drawn down through the deep ring and along the inguinal canal to emerge at the external abdominal ring. It is ready for placement in the scrotal pouch.

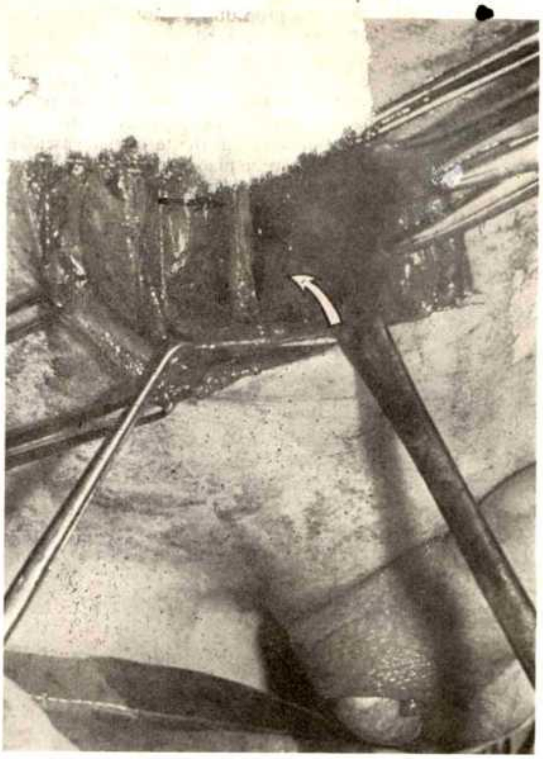

Fig. 7. An operative photograph which shows the typical appearance of the testicular vessels after placement of the testicle in the scrotal pouch. Although there has been no interference with the anatomy of the inguinal canal, the vessels take an almost straight line towards the testicle. This, view, which cannot be obtained during a Bevan orchidopexy, shows that there is no appreciable lateral deviation of the vessels as they pass through the internal ring. The emphasis which some writers (Gross, 1953; Whitaker, 1976) place on the need to incise the posterior wall of the inguinal canal in order to overcome this lateral deviation appears to be misplaced.

brim and traced it upwards to a point on the posterior aspect of the peritoneum at which it met the testicular vessels, but there was no sign of a testicle. Such a finding leaves no doubt that the testicle is absent.

8. Continuing the operation from paragraphs 5 or 6, the next step is to draw the testicle through the inguinal canal, and this is most easily done by lifting the lower skin flap and dissecting downwards with scissors in the subcutaneous plane to expose the superficial inguinal ring. A curved artery forceps is passed through the ring and up the inguinal canal to emerge at the deep ring. The tunica vaginalis is incised to expose the testis and the cut edge of the tunica is grasped by the artery forceps and used to draw the testicle down the inguinal canal and out through the external ring (*Fig.* 6).

9. When the extraperitoneal approach is used for a testicle near the superficial inguinal ring, we usually do not attempt to draw the testicle back into the abdomen as described in paragraph 5. The separation of the processus vaginalis, ligation of the neck of the processus and retroperitoneal dissection of the vessels and vas are completed as described above. Then the superficial inguinal ring is exposed by retraction of the lower skin flap and the testicle is expressed from the inguinal canal and gently held up. Freeing of all cremasteric and other fibrous bands holding the testicle proceeds as in a Bevan orchidopexy and when this is complete, the spermatic cord, which has already been freed within the abdomen, can be drawn out of the external ring. This combined exposure, from above and below the inguinal canal, allows an excellent view and very precise dissection.

10. A pouch is now formed in the scrotum as described by Petrivalsky (1931). The index finger breaks down the fibrous bands that obstruct the entrance to the scrotum and is passed to the lower pole of the scrotal sac. Holding the skin stretched over the index finger, a transverse incision about 1 cm long is made, through skin and dartos only, in the lower half of the scrotum. By using curved mosquito forceps as a dissector, a pocket is now formed between the skin and the deep fascia of the scrotum which will be large enough to hold the testicle comfortably. A 0·5-cm incision is made through the deep fascia on to the index finger and a curved mosquito forceps is passed into this incision, through the scrotum, to the region of the superficial ring. The forceps picks up an edge of the tunica and the testicle is then drawn down to the scrotum and gently pulled through the incision in the deep fascia which closes behind the testicle and prevents it retracting (*Fig.* 7). The testicle is now settled into the pouch and the skin closed over the top of it with interrupted mattress sutures of 3/0 catgut, which take a small bite of the tunica albuginea.

11. Finally, the incision is closed with sutures of 3/0 or 2/0 polypropylene according to the age of the boy. Interrupted sutures are placed in the transversus/internal oblique layer and then in external oblique: the knots are placed on the inner side of this aponeurosis.

Alternative technique

Fortunately, it is not necessary to decide on the use of the extraperitoneal approach before commencing an orchidopexy, although it is usually possible to do so. If the operation has been commenced in the usual way, through the inguinal canal, and the testicle proves unexpectedly difficult to mobilize, it is simple to change over to the extraperitoneal approach without making a new skin incision.

The upper skin edge is lifted and the skin and subcutaneous fat are dissected off the surface of external oblique until there is sufficient clearance to allow the muscle-splitting incision described in paragraph 2 to be used. This involves some firm [illegible] re is n[illegible]

[illegible] The [illegible]
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bundle has allowed the testicle [illegible] d in a good position in the scrotum: later examination has shown that these testicles have remained in the scrotum and are of good size.

Results

The circumstances in which we first used the extraperitoneal approach have been previously described (Gatenby et al., 1975). These initial results encouraged us to continue to use this approach for all impalpable testicles. It has also been used for testicles that, lying within an inguinal hernial sac, can be massaged out of the inguinal canal and then be palpated over the superficial inguinal ring—what some call 'emergent' testicles.

Over a period of nearly 4 years, to September 1977, our unit has attempted orchidopexy in 196 patients of between 4 weeks and 16 years of age. Nineteen patients have had a bilateral operation, so a total of 215 explorations has been made.

On 123 occasions a palpable testicle (usually of superficial inguinal ectopic type) was mobilized by the Bevan technique and placed in a good position in the scrotum. Although in some cases these operations required wide dissection at and through the internal ring, on no occasion did we divide the inferior epigastric artery or open up the posterior wall of the inguinal canal. On follow-up all these testicles lay in a good position.

On 92 occasions the extraperitoneal approach was chosen. In one boy a Pfannenstiel incision was used to perform bilateral extraperitoneal orchidopexy and in another a La Roque transperitoneal incision was used, but neither of these approaches was found to be so convenient as the muscle-splitting incision, which was used for the other 89 explorations.

In 6 out of the 92 extraperitoneal operations orchidopexy was not possible. One testicle was found on the posterior abdominal wall 4 cm above the internal ring; it could not be adequately mobilized and it was removed (the contralateral testicle was normal). In 5 explorations no testicle was found, although the vas deferens was identified (Tibbs, 1961). In 2 cases the vas terminated in the abdomen at a point where it met the spermatic vessels. In the 3 other cases both vas and vessels were traced to the scrotum but no testicle was found. These seemed likely to have been cases of testicular atrophy following an undiagnosed neonatal torsion.

In the remaining 86 extraperitoneal operations a testicle was found and mobilized and in 85 the testicle was placed in a scrotal pouch. Of these 86 testicles, 6 were abdominal, 42 lay at the deep ring or in the inguinal canal and 38 were 'emergent'. An inguinal hernial sac was present in every case. Seven testicles had to be left in a rather high position but on later examination 5 were found to have taken up a normal position in the scrotum. Four of the 85 testicles successfully placed had been previously fixed over the pubic bone by a Bevan orchidopexy: when re-explored, the extraperitoneal approach was found to be advantageous because it allowed easy identification of the adherent point at which the neck of the sa[illegible] been ligated, and of the vessels and [illegible] th[illegible] helped subsequent dissection of these [illegible] the scar tissue in the inguinal canal. The [illegible] e not placed in the scrotum was an abdominal testicle that had to be left over the pubic bone for later re-exploration.

Seventy-six of the 86 extraperitoneal operations were performed more than 1 year before the time of writing and the results in 73 have been reviewed more than 1 year after operation. The testicle that had to be left outside the external ring remains there but the other 72 testicles all lie within the scrotum (although 4 of them lie in the upper half). Fifteen testicles were noted to be appreciably smaller than the opposite testicle at the time of operation and in 11 of these palpable growth has occurred. One of these 15 testicles was very small at operation and remains very small. The great majority of the other 57 testicles have kept pace with the growth of the opposite testicle, and none was thought to be smaller than at the time of operation.

There has been no instance of any weakness of the muscle-splitting incision and the healed scar is inconspicuous.

On four occasions appendicectomy was also indicated when a right extraperitoneal orchidopexy was being performed; the appendix was readily removed through the incision.

Discussion

Modern writers on orchidopexy (Whitaker, 1976; Williams, 1977) describe a procedure that does not differ in essentials from the operation illustrated and described by Bevan in 1903. Both Whitaker and Williams state that when there is difficulty a second higher incision can be used, but this incision is not further described. Others (Florence, 1957; Bourque, 1961) have already drawn attention to the advantages of an extraperitoneal approach, but they have used midline or Pfannenstiel incisions. The muscle-splitting incision gives equally good exposure through a smaller wound that heals strongly and causes very little pain. We now have no hesitation in using this approach whenever a testicle is impalpable or 'emergent'.

The results are most encouraging. There is no doubt in our minds that the extraperitoneal approach was instrumental in allowing many of the impalpable testicles to be placed in the scrotum in one stage. In the years before we began using this approach there was a fairly steady failure rate (i.e. we failed to place the testicle in the scrotum at the first operation) of 10 per cent for orchidopexy in our unit. Over the past 4 years in performing 210 orchidopexies the only 2 failures were an orchidectomy on an abdominal testicle and a case in which one testicle was left over the pubic bone.

The value of the approach was well seen in 6 infants under 2 years of age in whom it was necessary to operate on an inguinal hernia and when there was also incomplete testicular descent. The delicacy of the processus vaginalis at this age is well known, and it is easy to tear it near the deep ring, where repair of the rent can be very difficult. Both herniotomy and orchidopexy are made easier by the extraperitoneal approach, the neck of the sac being readily isolated when approached from above. Our youngest patient was 4 weeks old; the operation was straightforward and a year later the testicle is of good size and in a normal position in the scrotum.

The advantages of the approach can be summarized as follows:

1. The incision gives a good access, is comfortable postoperatively and heals strongly. A change can be made from the standard approach to the abdominal muscle-splitting incision during the operation without making a second skin incision.

2. The exposure of the retroperitoneal area which is obtained allows extensive mobilization of the testicular vessels and vas deferens. A wide search can be made for an abdominal testicle, and this allows a confident diagnosis of anorchia to be made if the search for the testicle proves negative. Neither of these aims can be consistently achieved through the Bevan exposure.

3. The ability to dissect out the hernial sac and separate it from the vessels above the inguinal ligament makes this part of the operation easier, especially in infants. This ability, and the easy mobilization of the vessels and the vas, removes the need to retract and enlarge the deep inguinal ring or to incise the posterior wall of the inguinal canal.

4. By the use of the Bevan or the extraperitoneal operation, 210 explorations revealed the presence of a testicle, 208 of which were placed in the scrotum. This is a great improvement on our former results. The position of the testicles has been seen to be maintained over one or more years and growth of the testicle is common.

So far we have not discovered any disadvantages that attend the use of the abdominal approach and it has now become an established procedure in this hospital.

Acknowledgements

We are indebted to Marion Fordyce for much secretarial assistance and to Nigel Lukins of the Department of Medical Illustration, University of Aberdeen, for the illustrations.

References

BEVAN A. D. (1899) Operation for undescended testicle and congenital inguinal hernia. *JAMA* **33**, 773–775.

BEVAN A. D. (1903) Surgical treatment of undescended testicle. *JAMA* **41**, 718–723.

BEVAN A. D. (1929) The operation for undescended testis. *Ann. Surg.* **90**, 847–858.

BOURQUE J.-P. (1961) A new technique for orchidopexy. Report to a meeting of the Canadian Urological Association, Montreal, 14 June 1961.

CHEATLE G. L. (1921) An operation for inguinal hernia. *Br. Med. J.* **2**, 1025–1026.

DAVISON C. (1911) The surgical treatment of undescended testicle. *Surg. Gynecol. Obstet.* **12**, 283–288.

DOUGALL A. J., MACLEAN N. and WILKINSON A. W. (1974) Histology of the maldescended testis at operation. *Lancet* **1**, 771–774.

FIROR H. V. (1971) Two-stage orchidopexy. *Arch. Surg.* **102**, 598–599.

FLORENCE T. J. (1957) Surgical approach to cryptorchidism. *Transactions of Southeast Section American Urology Association*, pp. 89–91.

FOWLER G. R. (1900) New and improved method of entering the abdominal cavity in the ileo-caecal region. *Medical News* **76**, 321–324.

GATENBY A., STEWART D. J. and JONES P. F. (1975) Preperitoneal approach for orchidopexy. *J. R. Coll. Surg. Edinb.* **20**, 244–247.

GROSS R. E. (1953) *The Surgery of Infancy and Childhood.* Philadelphia, Saunders, pp. 467–481.

GROSS R. E. and REPLOGLE R. L. (1963) Treatment of the undescended testicle: opinions gained from 1767 operations. *Postgrad. Med.* **34**, 266–270.

JACOBSON C. E. (1966) Midline approach to orchidopexy. *J. Urol.* **95**, 74–76.

LA ROQUE G. P. (1931) A modification of Bevan's operation for undescended testicle. *Ann. Surg.* **94**, 314–317.

LIPTON S. (1961) Use of the Cheatle–Henry approach in the treatment of cryptorchidism. *Surgery* **50**, 846–848.

PERSKY L. and ALBERT D. J. (1971) Staged orchidopexy. *Surg. Gynecol. Obstet.* **132**, 43–45.

PETRIVALSKÝ J. (1931) Zur Behandlung des Leistenhodens. *Zentralbl. Chir.* **58**, 1001–1005.

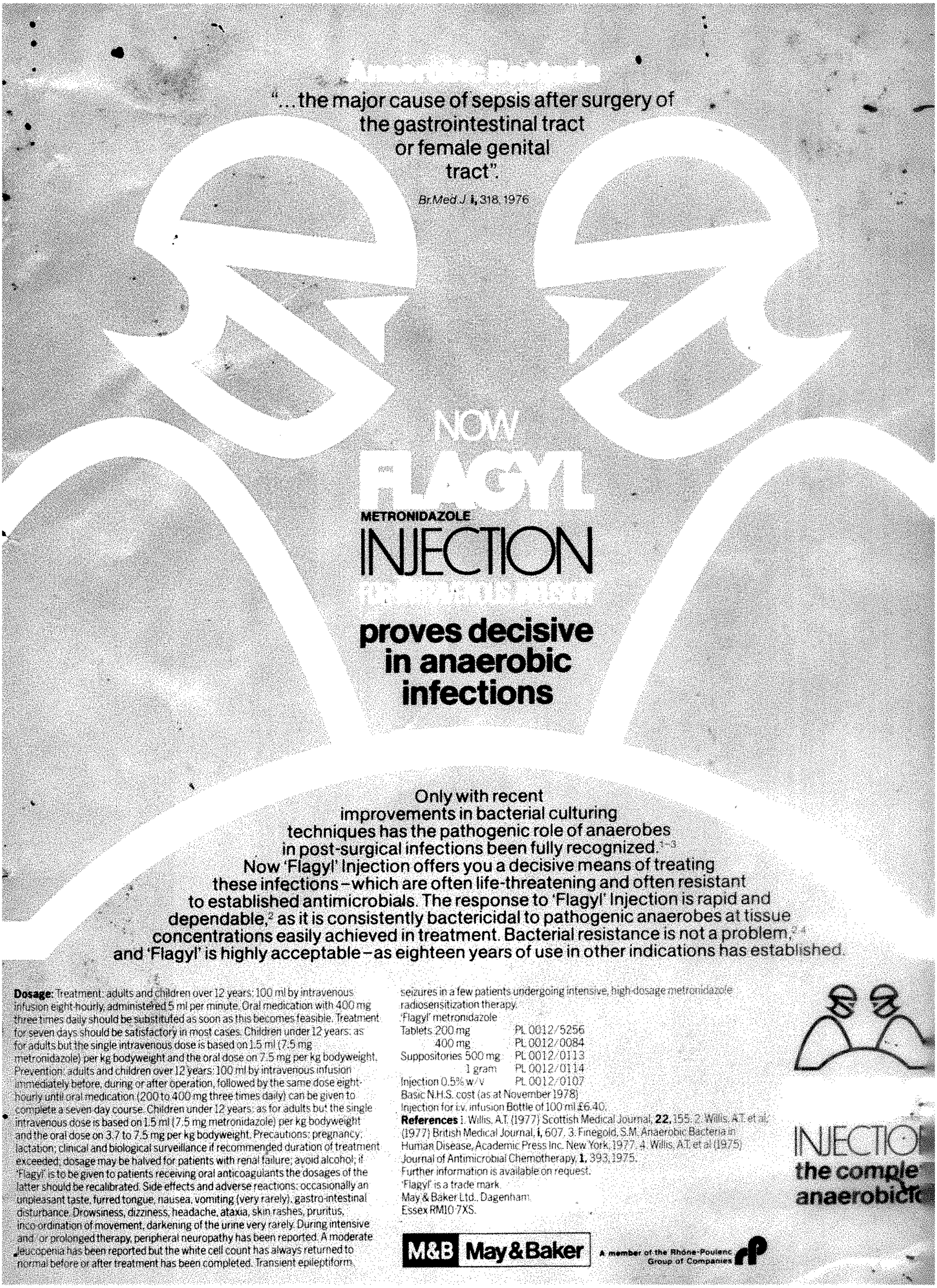
TIBBS D. J. (1961) Unilateral absence of the testis. *Br. J. Surg.* **48**, 601–608.

WEIR R. F. (1900) Improved operation for acute appendicitis. *Medical News* **76**, 241–242.

WHITAKER R. H. (1976) Congenital disorders of the testicle. In: BLANDY J. (ed.) *Urology*. Oxford, Blackwell Scientific, p. 1170.

WILLIAMS D. I. (1977) Orchidopexy. In: WILLIAMS D. I. (ed.) *Operative Surgery: Urology.* London, Butterworths, pp. 402–406.

Paper accepted 26 June 1978.



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References 1. Willis, A.T. (1977) Scottish Medical Journal, **22**, 155. 2. Willis, A.T. et al. (1977) British Medical Journal, **i**, 607. 3. Finegold, S.M. Anaerobic Bacteria in Human Disease, Academic Press Inc. New York, 1977. 4. Willis, A.T. et al (1975) Journal of Antimicrobial Chemotherapy, **1**, 393, 1975.

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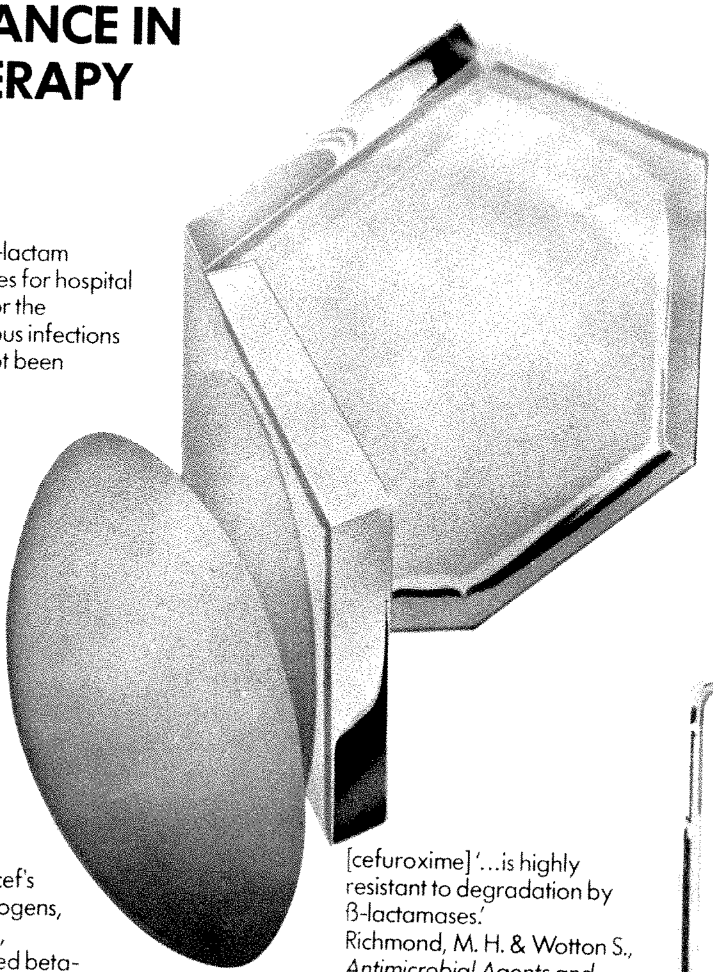

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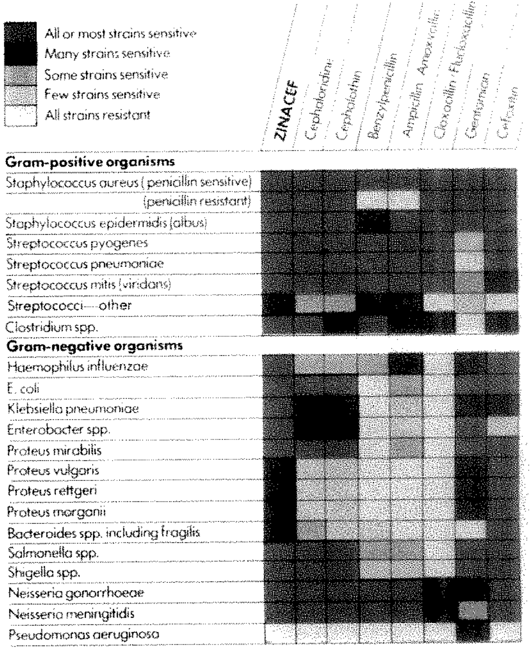

▓ All or most strains sensitive
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▒ Some strains sensitive
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Gram-positive organisms								
Staphylococcus aureus (penicillin sensitive)	▓	▓	▓	▓	▓	▓	▓	▓
(penicillin resistant)	▓	▓	▓	░	░	▓	▓	▓
Staphylococcus epidermidis (albus)	▓	▓	▓	█	▓	▓	▓	▓
Streptococcus pyogenes	▓	▓	▓	▓	▓	▓	░	▓
Streptococcus pneumoniae	▓	▓	▓	▓	▓	▓	░	▓
Streptococcus mitis (viridans)	▓	▓	▓	▓	▓	▓	▒	▓
Streptococci—other	█	▒	▒	█	█	░	░	░
Clostridium spp.	▓	▓	█	▓	█	█	░	▓
Gram-negative organisms								
Haemophilus influenzae	▓	░	░	░	█	░	▓	▓
E. coli	▓	▓	▓	░	▒	░	▓	▓
Klebsiella pneumoniae	▓	█	█	░	░	░	▓	▓
Enterobacter spp.	▓	█	█	░	░	░	▓	░
Proteus mirabilis	▓	▓	▓	░	▒	░	▓	▓
Proteus vulgaris	█	░	░	░	░	░	▓	▓
Proteus rettgeri	█	░	░	░	░	░	▓	▓
Proteus morganii	█	░	░	░	░	░	▓	▓
Bacteroides spp. including fragilis	█	▒	░	░	░	░	░	▓
Salmonella spp.	▓	▓	▓	▒	▒	░	▓	▓
Shigella spp.	▓	▓	▓	░	▒	░	▓	▓
Neisseria gonorrhoeae	▓	▓	▓	▓	▓	█	█	▓
Neisseria meningitidis	▓	▓	▓	▓	▓	█	▒	▓
Pseudomonas aeruginosa	□	░	░	░	░	░	█	░

ZINACEF

Prescribing information

Presentation
Vials of 250mg, 750mg and 1·5 gram and infusion pack of 1·5 gram. All containing cefuroxime as cefuroxime sodium.

Indications
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Dosage
Adults: Generally 750mg t.d.s. i.m. or i.v. Severe infections 1·5 gram t.d.s. i.v. Frequency of injections can be increased to six-hourly if necessary.
Infants and children: 30 to 100mg/kg/day in three or four divided doses. 60mg/kg/day will be appropriate for most infections.
Neonates: 30 to 100mg/kg/day in two or three divided doses.
Gonorrhoea: Single dose of 1·5 gram (2 x 750mg i.m. into different sites).

Contra-indications
Hypersensitivity to cephalosporins.

Precautions
Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins.
As with all drugs, Zinacef should be administered with caution during the early months of pregnancy.
Zinacef does not interfere with enzyme-based tests for glycosuria.
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As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms.
Zinacef should not be mixed in the syringe with aminoglycoside antibiotics.
Reduce dosage when renal function is markedly impaired.
Cephalosporins at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as frusemide, as these combinations are suspected of adversely affecting renal function. Clinical experience with Zinacef has shown that this is not likely to be a problem at the recommended dose levels.

Side effects
Adverse reactions are rare and generally mild and transient, e.g., rashes, gastro intestinal disturbance, candida intertrigo, decreased haemoglobin concentration, eosinophilia, a positive Coombs' test, transient rises in serum liver enzymes and transient pain (after i.m. injection).

Storage
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Br. J. Surg. Vol. 66 (1979) 19-22

The medical management of renal artery stenosis in transplant recipients

S. J. JACHUCK, R. WILKINSON, P. R. ULDALL, R. W. ELLIOTT, R. M. R. TAYLOR AND P. M. HACKING*

SUMMARY

The investigation, management and clinical course of 12 patients developing stenosis of the renal artery following transplantation are described. The possible aetiology of the three arteriographic patterns of stenosis is discussed. Surgical correction of graft arterial stenosis is difficult and may lead to graft loss, whereas the outcome with antihypertensive drug treatment with or without anticoagulants is good. Surgery should only be contemplated if medical treatment is failing or if renal function is deteriorating.

STENOSIS of the graft artery with hypertension is diagnosed in 3–16 per cent of renal transplant recipients (Doyle et al., 1975; Fine, 1975; Lindsey et al., 1975; Belzer and Salvatierra, 1976; Schacht, 1976). Although in some centres surgical repair is usually successful (Belzer and Salvatierra, 1976), most centres report a substantial failure rate, often with loss of the graft (Doyle et al., 1975; Fine, 1975; Schacht et al., 1976). This has led us to examine the results of medical treatment of renal artery stenosis in transplant recipients.

Patients and methods

Of 239 transplants performed in Newcastle between January 1972 and April 1976, renal artery stenosis with hypertension has been diagnosed in 12 (5 per cent). The clinical details of these patients before transplantation are given in *Table I* and following grafting in *Table II*. Transplant arteriography was performed because of severe hypertension. In 11 of the patients found to have renal artery stenosis a bruit was audible over the kidney or femoral artery. Renal arteriography was repeated after 1 year in those treated conservatively. Renal biopsy was performed in 4 and histological examination of the nephrectomy specimen in 3.

Angiographic findings and histology

Group 1: In 7 patients there was stenosis at the site of the anastomosis with normal intrarenal vessels (*Fig.* 1). Biopsy was performed in 3 of these patients and showed normal histology (*Table II*).

Group 2: Stenosis of the allograft artery beyond the anastomosis was seen in 2 patients with normal small vessels (*Fig.* 2). Renal biopsy was performed in one of these and the findings were normal.

Group 3: In the remaining 3 patients stenosis at the site of anastomosis was accompanied by irregularity of small vessels (*Fig.* 3). In the 2 patients biopsied there was fibrin deposition and fibroblastic proliferation in the arcuate and interlobular arteries, suggesting vascular rejection.

Management and outcome

Surgical: The renal artery was explored in 3 patients. In all cases it was enveloped in dense fibrous tissue. In 1 patient a saphenous vein bypass graft was performed, but the graft subsequently thrombosed and the kidney was lost. In the second case repair was considered impossible and nephrectomy was performed because at that time (1972) it was considered hazardous to attempt long term medical treatment. In the third case (H. W.) repair was not possible because of dense fibrosis. The kidney was left *in situ*; it continues to function at 1 year and control of hypertension is satisfactory.

Table I: PRE-TRANSPLANT CLINICAL DETAILS OF 12 PATIENTS SUBSEQUENTLY DEVELOPING STENOSIS OF THE RENAL ARTERY TO THE TRANSPLANT

Patient	Mean recumbent b.p. during last month of dialysis (mmHg) S	D	Original kidney disease	Bilateral nephrectomy
R. A.	140	80	Malignant hypertension	No
E. H.	170	100	Chronic pyelonephritis	No
K. B.	170	100	Glomerulonephritis	No
N. C.	170	115	Analgesic nephropathy	No
B. W.	200	120	Glomerulonephritis	No
S. D.	160	100	Glomerulonephritis	Yes
M. V.	100	70	Analgesic nephropathy	No
A. W.	150	90	Glomerulonephritis	Yes
H. W.	190	105	Malignant hypertension	No
E. Y.	160	100	Glomerulonephritis	Yes
K. P.	180	120	Malignant hypertension	Yes
S. O.	180	90	Glomerulonephritis	Yes

S, Systolic; D, diastolic.

Antihypertensive drugs alone: One patient died following a grand mal fit while being prepared for surgery, in 1 patient hypertension was controlled but nephrectomy was performed (*see above*), but 3 patients, all in group 1, continue with satisfactory blood pressure and good renal function more than a year after diagnosis of stenosis (*Table II*).

Antihypertensive drugs, warfarin and dipyridamol: In 5 patients (3 in group 1, 1 in group 2 and 1 in group 3) blood pressure control was difficult initially and warfarin and dipyridamole were added to the treatment regimen after inpatient control of severe hypertension. Thereafter control appeared easier and renal function did not deteriorate appreciably over the period of follow-up, except in patient S. O. in whom deterioration followed an episode of rejection 3 years after the diagnosis of arterial stenosis (*Table II*). There had been no progression of the arterial stenosis in the 4 patients re-examined after 1 year.

Antirejection treatment

The 2 patients in grou [illegible] ith histological evidence of rejection were treated with 3 [illegible] methylprednisolone over 3 days. In both patients the [illegible] vessels had reverted to normal on repeat angiogra [illegible] ut hypertension and the large vessel stenoses persisted, suggesting that the latter were responsible for the hypertension.

Discussion

Arteriographic patterns of the type we have encountered have been described by other groups (Smellie et al., 1969; Morris et al., 1971). Stenosis at the site of anastomosis (group 1) is usually attributed to trauma inflicted on the artery before or at the time of anastomosis (Smellie et al., 1969), although Belzer and Salvatierra (1976) have suggested that the use of silk suture material may be responsible. More distal stenosis (group 2) has been attributed to kinking of a

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Correspondence to: R. Wilkinson.

Table II: POST-TRANSPLANT CLINICAL DETAILS OF 12 PATIENTS WITH HYPERTENSION AND STENOSIS OF THE ARTERY TO THE TRANSPLANT

Patient and group	Anastomosis	Initial angiographic findings			Angiogram after 1 yr	Histo-pathology	Treatment	Follow-up from diagnosis of stenosis (yr)	Blood pressure (mmHg)		Serum creatinine (µmol/l)	
		Anastomosis	Allograft artery	Intrarenal vessels					Initial	Final on medical treatment	Initial	Final on medical treatment
R.A. 1	End-to-side	Stenosis	Normal	Normal	—	No rejection	Failed bypass nephrectomy	0·2	200/130	150/90	140	140
E. H. 1	End-to-side	Stenosis	Normal	Normal	—	—	Antihypertensives	4·0	170/115	130/90	100	80
K. B. 1	End-to-end	Stenosis	Normal	Normal	Unchanged	—	Antihypertensives	2·5	160/110	130/90	110	150
N. C. 1	End-to-end	Stenosis	Normal	Normal	Unchanged	—	Antihypertensives and anticoagulants*	4·0	190/105	140/70	140	120
B. W. 1	End-to-end	Stenosis	Normal	Normal	Unchanged	Mild rejection	Antihypertensives and anticoagulants	4·0	180/120	120/90	120	195
S. D. 1	End-to-end	Stenosis	Normal	Normal	Unchanged	—	Antihypertensives and anticoagulants	4·0	170/115	130/80	110	115
M. V. 1	End-to-end	Stenosis	Normal	Normal	—	No rejection	Antihypertensives	4·0	200/110	150/80	220	185
A. W. 2	End-to-side	Normal	Stenosis 1 cm beyond anastomosis	Normal	—	No rejection (autopsy)	Antihypertensives Died following convulsions	0·3	220/140	220/130	140	150
H. W. 2	End-to-end	Normal	Stenosis 2 cm beyond anastomosis	Normal	—	—	Exploration only Antihypertensives and anticoagulants	1·0	240/150	140/92	120	130
E. Y. 3	End-to-side	Stenosis	Normal	Irregular	—	Vascular rejection	Nephrectomy	0·2	210/155	140/85	180	350
K. P. 3	End-to-side	Stenosis	Normal	Irregular	Intrarenal vessels normal	No rejection	Antihypertensives	4·0	190/115	140/90	110	120
S. O. 3	End-to-end	Stenosis	Normal	Irregular	Intrarenal vessels normal	Vascular rejection	Antihypertensives, anticoagulants and antirejection	4·0	170/110	160/90	120	290

* Anticoagulants, dipyridamole 200 mg t.d.s.; warfarin as required.

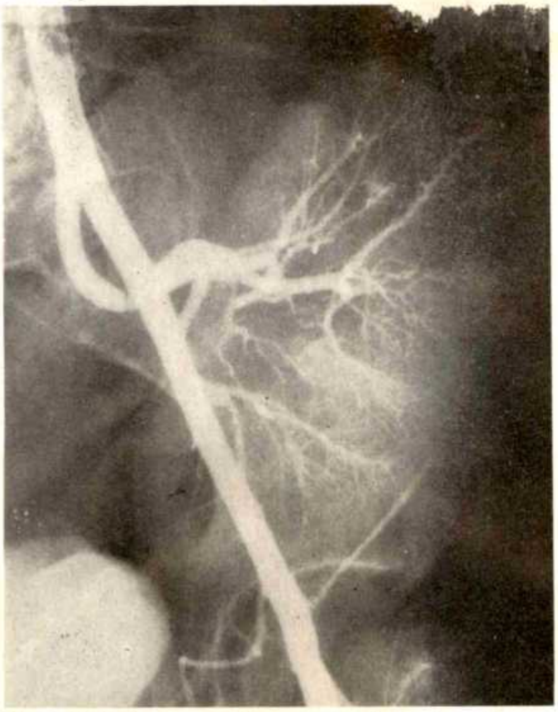

Fig. 1. Typical angiographic appearance in a patient in group 1. Stenosis is at the site of anastomosis and the intrarenal vessels are normal.

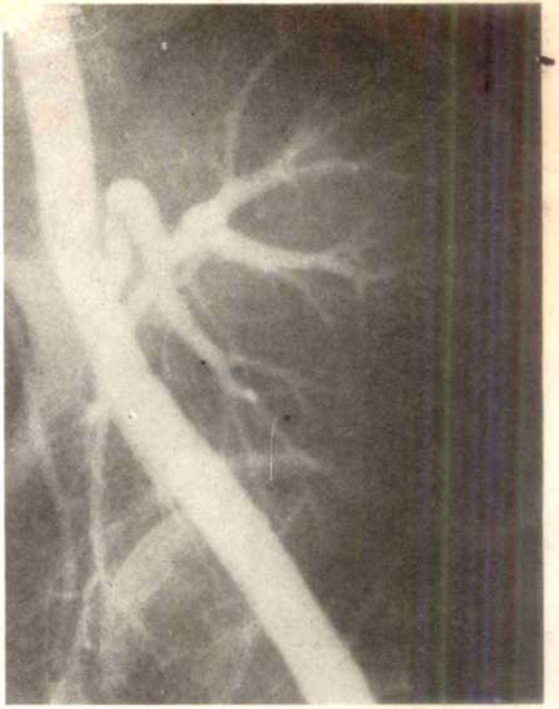

Fig. 2. In patients in group 2 there is stenosis of the allograft artery beyond the anastomosis with normal small vessels.

D25358

donor artery that is too long and also to the use of the end-to-side anastomosis (Morris et al., 1971). One of our patients with this type of stenosis (A. W.) had end-to-side anastomosis of renal to external iliac artery, but in the other (H. W.) the renal artery was anastomosed end to end to the internal iliac artery. Diffuse irregularity of intrarenal vessels is, as we have found, usually due to rejection (Morris et al., 1971). In 2 of our patients the donor was a child, but in only one of these cases was the stenosis at the anastomosis (E. Y.). In the other (A. W.) the stenosis appeared to be due to kinking and was apparently unrelated to the small calibre of the donor artery.

It is difficult to be certain that the hypertension was due to the demonstrated stenosis. Although one patient (H. W.) had been severely hypertensive before starting on dialysis, hypertension had not been a serious problem during dialysis and renin studies following transplantation revealed higher plasma renin activity in the left common iliac vein (the side of the transplant) than in the original renal veins. Five of the patients had been subjected to bilateral nephrectomy so that the diseased kidneys could not be incriminated. In 4 other patients hypertension had not been a problem during dialysis (*Table I*), making it unlikely that the diseased kidneys were the cause of the post-transplant hypertension. Two patients not subjected to bilateral nephrectomy (N. C. and B. W.) had been hypertensive on dialysis and it is difficult to be certain that the undoubted stenosis of the transplant artery was the cause of their post-transplant hypertension.

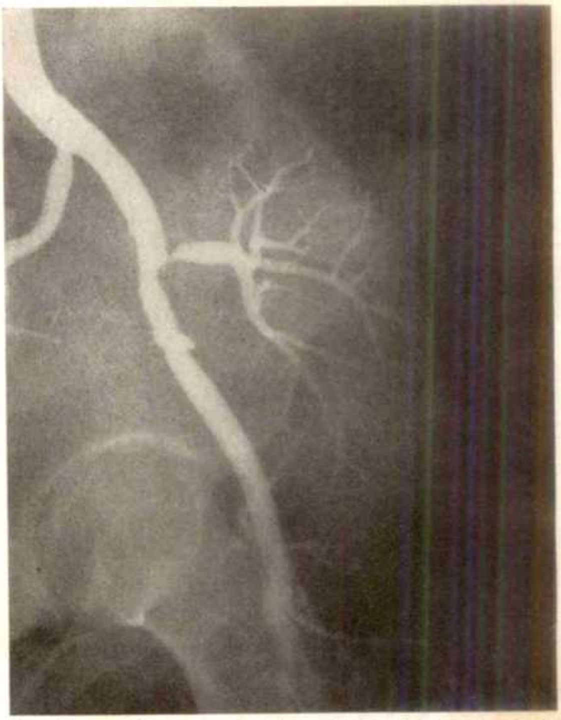

Fig. 3. Group 3 comprised patients with stenosis at the site of anastomosis accompanied by irregularity of small vessels.

In the 9 patients followed up for 1 year or more hypertension p[illegible] despite reduction of the dose of prednisone t[illegible] than 10 mg/day, suggesting that high steroid dosage was not the cause of hypertension. Renal function was good in 11 of the patients so that hypertension was not likely to be due to chronic vascular rejection.

It seems likely, therefore, that, in the absence of other detectable causes, the demonstrated renal artery stenosis was responsible for post-transplant hypertension in the majority of the 12 patients described. It is, of course, impossible to be certain of this except by observing the response to surgery.

Because of the coexistence of anastomotic stenosis and kidney rejection in two patients (E. Y. and S. O.), we thought it possible that transplant artery stenosis might be due, in some cases, to a local rejection phenomenon with adherence of platelets and deposition of fibrin. This provided the rationale for the addition of warfarin and dipyridamol to antihypertensive therapy. Even if this were not the mechanism it was thought that this treatment might delay the progression of stenosis. Whilst these patients did well, so also did 3 of the 5 patients treated with antihypertensive drugs alone (one other patient died and one was subjected to nephrectomy in this group). We are not able, therefore, to comment further on the role of these drugs in the treatment of transplant artery stenosis. However, a controlled trial of their use may be justified on the basis of our experience. A multicentre trial with all its difficulties would be necessary in view of the rarity of this complication of transplantation. Anticoagulants can, of course, only be given after blood pressure control has been achieved, if necessary with parenteral therapy.

Because of the rather poor results with surgical treatment of transplant artery stenosis (Doyle et al., 1975; Fine, 1975; Schacht et al., 1976) and the difficulty in determining the functional significance of any anatomical stenosis demonstrated (Gupta et al., 1976), most transplant surgeons consider surgery only if hypertension is accompanied by deteriorating renal function, as in one of our patients (M. V.), or if hypertension cannot be controlled medically. Our experience supports this approach and we have not lost a patient, nor indeed a kidney, from renal artery stenosis since the death of patient A. W., which occurred in 1972. Even patient M. V., who had slightly impaired renal function initially, has suffered no further reduction in function.

Transplant arteriography is worth while in patients with severe hypertension even if surgery is not contemplated, since (*a*) a positive diagnosis of arterial stenosis may spare the patient bilateral nephrectomy, (*b*) the initial arteriogram will give an indication of the feasibility of surgery should medical treatment fail, and (*c*) small vessel changes may be revealed that indicate the likelihood of vascular rejection and the need for antirejection treatment if this is confirmed by biopsy.

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References

BELZER F. O. and SALVATIERRA O. (1976) Renal transplantation: organ procurement, preservation and surgical management. In: BRENNER B. M. and RECTOR F. C. (ed.) *The Kidney*. Philadelphia, Saunders, pp. 1796–1818.

DOYLE T. J., MCGREGOR W. R., FOX P. S. et al. (1975) Homotransplant renal artery stenosis. *Surgery* **77**, 53–60.

FINE R. N. (1975). Renal transplantation in children. In: HAMBURGER J., CROSNIER J. and MAXWELL M. H. (ed.) *Advances in Nephrology*, 5. Chicago, Year Book, pp. 201–228.

GUPTA S. K., RAO T. K. S., BUTT K. M. H. et al. (1976) Renal artery stenosis in renal transplant recipients. Washington, DC, Clinical Dialysis and Transplant Forum Proceedings, pp. 162–167.

LINDSEY E. S., GARBUS S. B., GOLLADAY E. S. et al. (1975) Hypertension due to renal artery stenosis in transplanted kidneys. *Ann. Surg.* **181**, 604–610.

MORRIS P. J., YADAR R. V. S., KINCAID-SMITH P. et al. (1971) Renal artery stenosis in renal transplantation. *Med. J. Aust.* **1**, 1255–1257.

SCHACHT R. A., MARTIN D. G., KARALAKULASINGAM R. et al. (1976) Renal artery stenosis after renal transplantation. *Am. J. Surg.* **131**, 653–657.

SMELLIE W. A. B., VINK M. and HUME D. M. (1969) Angiographic investigation of hypertension complicating human renal transplantation. *Surg. Gynecol. Obstet.* **128**, 963–968.

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Arteriovenous grafts for vascula in haemodialysis

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SUMMARY

The outcome of 68 arteriovenous grafts placed in 46 patients requiring haemodialysis was studied over a period of 3·5 years. The biological grafts included autogenous saphenous vein, modified bovine carotid artery and human umbilical cord vein allograft, whereas the synthetic grafts comprised Sparks Dacron mandril, expanded reinforced polytetrafluoroethylene and knitted Dacron velour. These subcutaneous grafts were arranged as looped or straight configurations in the forearm or thigh. Of 59 grafts evaluated in patients with end-stage renal failure, only 48 per cent of the forearm grafts performed well, compared with 85 per cent of the thigh grafts. Although only 38 per cent of the looped grafts were successful, 78 per cent of the straight grafts functioned satisfactorily. Synthetic grafts suffered less serious complications than the commercial biological grafts.

MAINTAINING easy access to the bloodstream is both the keystone and Achilles heel of long term haemodialysis in end-stage renal failure. The most popular means of vascular access for close on two decades have been the external arteriovenous or Scribner shunt (Quinton et al., 1960) and the internal arteriovenous or Cimino–Brescia fistula (Brescia et al., 1966). Unfortunately, these primary procedures to obtain access to the circulation may fail sooner or later because of thrombosis, infection or inadequacy of the blood vessels. When all the forearm and ankle vessels have been obliterated by repeated primary procedures, then continued intermittent haemodialysis has been made feasible through the development of second-stage procedures, which include the implantation of subcutaneous arteriovenous grafts. This paper records the results obtained in one centre using a variety of grafts for continued haemodialysis in problem patients.

Table I: INDICATIONS FOR AN ARTERIOVENOUS GRAFT

Cimino–Brescia fistula impossible when forearm vessels:
  (*a*) obliterated by previous infusions, shunts or fistulas
  (*b*) indiscernible because of obesity or cachexia
  (*c*) unsuitable because of small calibre
Inadequate development of veins by arteriovenous fistulas
Scribner shunt not feasible when ultimate fistula fails
Imminent kidney transplant unlikely when ultimate fistula or shunt fails.

Table II: ARTERIOVENOUS GRAFTS IMPLANTED JUNE 1974 TO DECEMBER 1977

Sparks mandril (Dacron)	11	
Expanded reinforced PTFE (Gore-Tex)	22	
Knitted Dacron velour (Vasculour-D)	7	
Autogenous saphenous vein	8	
Human umbilical cord vein allograft (HUCVAG)	6	
Bovine carotid artery	14	
Ficin-digested		4
Gluteraldehyde-treated		5
Antibiotic-treated		5
Total	68	

Patients and methods

During the period of study, extending from June 1974 to December 1977, 68 arteriovenous grafts were implanted subcutaneously in 46 patients. The group comprised 19 men and 27 women, aged between 15 and 64 years, with an average age of 41. Apart from 5 cases with disseminated cancer of bronchus or bladder, all patients had end-stage renal failure. The 5 exceptions were scheduled for magnesium depletion in an attempt to control their spreading cancer. The indications for establishing a subcutaneous arteriovenous graft are listed in *Table I*. The number of previous first-stage vascular access procedures undertaken in each patient varied between none and 9, with a mean of 3·7.

The types and number of vascular grafts used in the study are listed in *Table II*. All grafts had an internal diameter of about 6 mm. The synthetic prostheses used were the Sparks Dacron mandril (American Hospital Supply UK Ltd) (*Fig*. 1), expanded microporous reinforced polytetrafluoroethylene (PTFE) or Gore-Tex (W. L. Gore UK Ltd) (*Fig*. 2) and knitted Dacron velour or Vasculour-D (USCI International Ltd) (*Fig*. 3). The biological grafts used were reversed autogenous saphenous vein, dialdehyde-treated human umbilical cord vein allograft or HUCVAG (Gene-Tec Scientific Ltd) (*Fig*. 4), ficin-digested bovine carotid artery graft or Surgikos Artegraft (Johnson and Johnson Ltd) (*Fig*. 5), gluteraldehyde-treated and antibiotic-treated bovine carotid artery grafts (Yorkshire Regional Tissue Bank) (*Figs*. 6, 7). In preparation of the two last-mentioned grafts, fresh bovine carotid arteries collected from the local abbatoir were treated in alternative ways: the first group was immersed in 0·5 per cent phosphate-buffered gluteraldehyde solution for 48 h and then stored in the solution. The second group was immersed in Medium 199 (Gibco Bio-cult Ltd) in which was dissolved gentamicin 4 mg/ml, methicillin 10 mg/ml, erythromycin 6 mg/ml, mycostatin 2500 units/ml and fetal calf serum to a concentration of 10 per cent. The arteries were stored in the solution at 4 °C for no longer than 5–6 weeks.

If the vessels of either forearm were judged to be inadequate, then the graft was placed in the thigh. In the forearm and thigh, the graft was usually arranged as a straight configuration, but when poor distal forearm vessels did not permit a straight configuration, then a loop based on the cubital fossa was fashioned. It was decided to place all the commercial bioprostheses in the thigh.

For a forearm loop, the brachial artery was bridged to the widest vein in the cubital fossa, the loop extending to the distal forearm. For a straight forearm configuration an appropriate vessel in the distal third of the forearm was connected to an antecubital vessel. In the thigh the common femoral artery was usually connected to the superficial femoral vein in the distal part of Hunter's canal. During the early phase of the study, a few thigh loops based on the femoral vessels were established, the loops extending to mid-thigh level.

The vascular suture used was 5/0 or 6/0 Prolene (Ethicon Ltd). Usually an interval of 10–14 days was allowed before a graft was cannulated for haemodialysis, so that the surgical wounds could heal. Many of the patients underwent haemodialysis at their homes.

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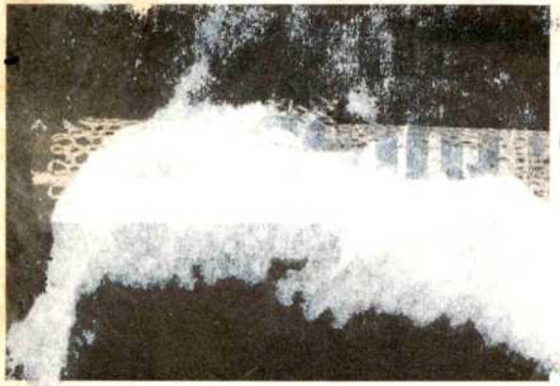

Fig. [illegible] Sparks mandril: two tubes of knitted Dacron supported by an inner silicone rod of 6 mm internal diameter.

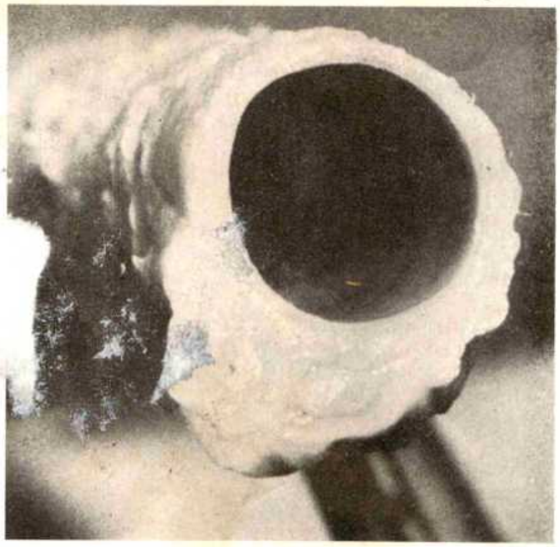

Fig. 4. Human umbilical cord vein allograft, 6 mm internal diameter.

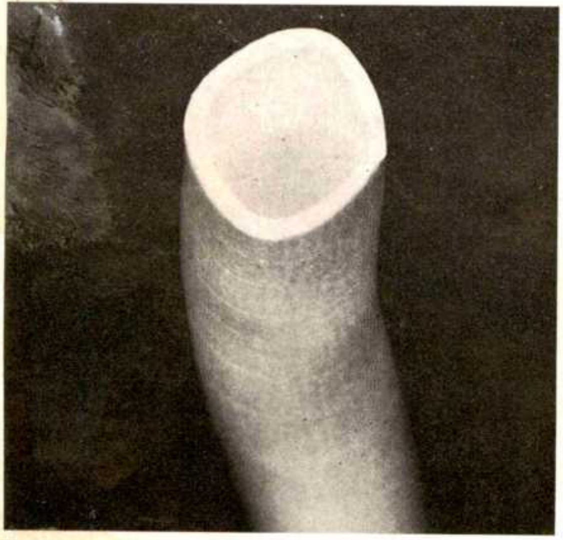

Fig. 2. Gore-Tex: expanded reinforced PTFE, 6 mm internal diameter.

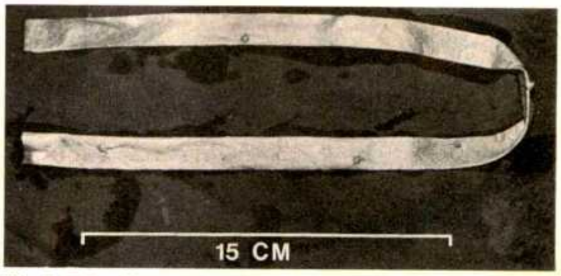

Fig. 5. Ficin-digested bovine carotid artery graft (Surgikos Artegraft).

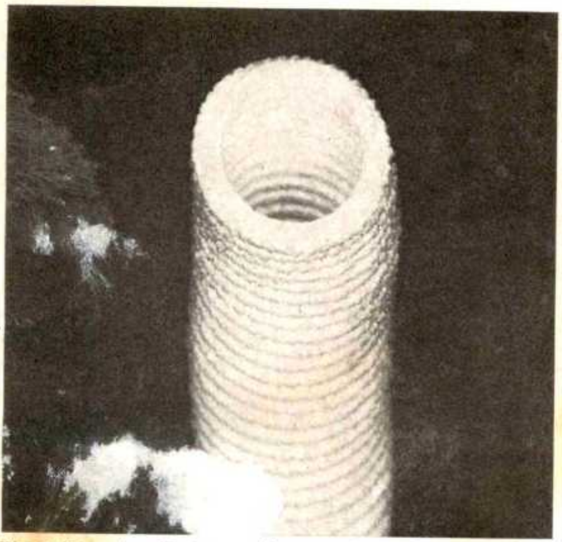

Fig. 3. Vasculour-D [illegible] Dacron velour, 6 mm internal diameter.

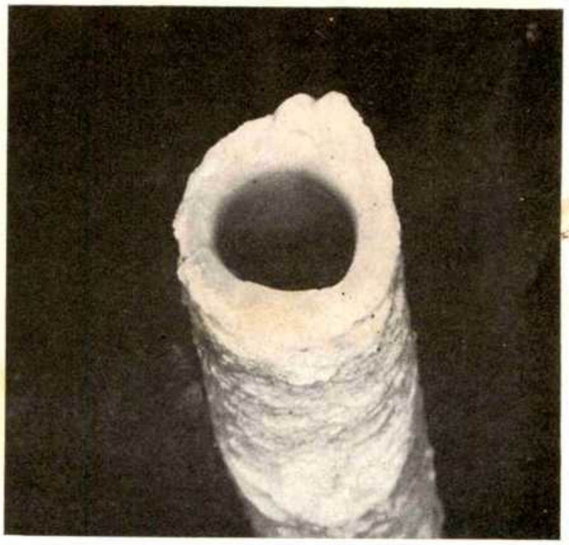

Fig. 6. Gluteraldehyde-treated bovine carotid artery graft, 6 mm internal diameter.

Results

Patency and function (*Table III*)

Primary failure of a graft was defined as the inability of the prosthesis to support even a single dialysis session because of thrombosis, inadequacy or sepsis.

Autogenous saphenous vein grafts: Two looped and 2 straight grafts thrombosed during the first postoperative week. A solitary thigh loop and a forearm loop were patent for 3 and 13 months respectively, and supported an average of 90 dialysis sessions. The 4 straight grafts in the forearm did worse, remaining patent for about 3 months, supporting about 62 dialysis sessions.

HUCVAG: Two grafts thrombosed at 1 and 2·5 months respectively, and were found to be too degenerative to salvage. Persistent sepsis of one graft prevented its use for haemodialysis, and it was excised after 5 months because of secondary haemorrhage. Two further grafts became aneurysmal after 8 and 11 months respectively and were excised. One graft remains trouble-free at 12·5 months, supporting about 102 dialysis sessions.

Bovine carotid artery grafts (*ficin-digested grafts, Surgikos Artegraft*: The 4 grafts achieved a mean patency of 12·3 months, supporting about 129 dialysis sessions. One patient died of exsanguinating haemorrhage from a cannulation site after 11 months and a second graft had been patent for 5·5 months at the time of the patient's death. The third graft became aneurysmal and then thrombosed by 11 months. The fourth graft remained patent for 16·5 months and then had to be excised because of uncontrollable bleeding from cannulation sites.

Gluteraldehyde-treated grafts: Two straight grafts in the forearm thrombosed at 9 weeks and 5 months respectively. Two thigh grafts remain open after 8·5 months of function.

Antibiotic-treated grafts: Two patients in the group died in the early postoperative period. A forearm looped graft and 2 thigh grafts remain open after a minimum of 5 months, and have each supported about 60 dialysis sessions.

Sparks Dacron mandril: Five of the 11 grafts thrombosed at an early stage and never functioned. None of the arm or thigh loop grafts remained patent beyond 2 months. Two of the 3 thigh straight grafts remain trouble-free and open after 23 months.

Expanded PTFE grafts (*Gore-Tex*): Two of the 8 forearm straight grafts remain patent and functional at 8 and 9 months respectively. Three primary failures occurred within 14 days of operation because of poor arterial inflow. The 5 functioning grafts supported an average of 78 dialysis sessions. Four of the 5 forearm looped grafts functioned for an average of 3 months, but only 1 remains patent. On the other hand, the 9 thigh straight grafts functioned best of all, with a duration of patency varying from 4·5 to 17 months (mean patency of 10 months). Four grafts remain open, while 2 were removed because of infected cannulation sites and a further graft was excised because of brisk bleeding from cannulation sites. The occlusion of one graft at 4·5 months was most probably related to the extensive atheromatous disease of the femoral artery. The ninth graft was patent for 6·5 months at the time of the patient's death.

Knitted Dacron velour grafts (*Vasculour-D*): All 6 grafts implanted in the thigh in straight configuration have given trouble-free service. They remain patent after nearly 4 months and they have supported some 30 dialysis sessions. One forearm loop graft suffered primary failure due to inadequate arm vessels.

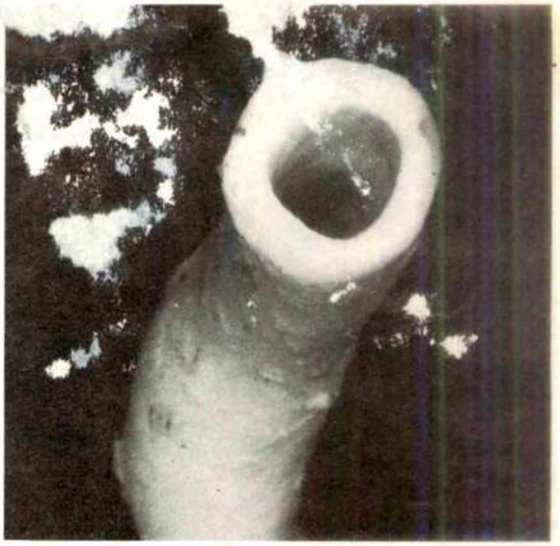

Fig. 7. Antibiotic-treated bovine carotid artery graft, 6 mm internal diameter.

Assessment of graft function: The success of each arteriovenous graft was assessed by the arbitrary criterion of whether the graft supported a minimum of 24 dialysis sessions. The grafts implanted in the 5 cancer patients and in those patients who died during the first 2 postoperative months were not included, leaving 59 grafts to be evaluated (*Table IV*). Whereas only 48 per cent of forearm grafts were successful, 85 per cent of thigh grafts performed well. Straight grafts enjoyed a measure of success of 78 per cent, compared with 38 per cent of looped grafts.

Complications (Table V)

Graft thrombosis: Thrombectomy was unsuccessful in the three clotted HUCVAGs because the grafts were too degenerative. Thrombectomy was successful in one bovine Artegraft, but not in a thrombosed gluteraldehyde-treated graft placed in the forearm. Only 3 of 6 attempts at thrombectomy performed in 5 of the Sparks mandril loop grafts succeeded.

None of 6 thrombectomies in 4 forearm Gore-Tex grafts achieved patency, but 9 such attempts with 5 thigh grafts established continued patency in all but one graft.

Deep vein thrombosis: One patient with a thigh Gore-Tex graft and another with a thigh Sparks mandril graft developed ipsilateral iliofemoral venous thrombosis.

Venous outflow problems: Five thigh grafts required reduction of their blood flow by partial ligation because of (*a*) gross unremitting oedema of the [illegible]eg (1 Gore-Tex and 2 bovine Art[illegible]afts); (*b*) venous pressure interfering [illegible] dialysis [illegible] HUVCAG); (*c*) increased ve[illegible] return produ[illegible] cardiac failure (1 bovine Arte[illegible]).

Arterial embolism: One pati[illegible] femorofemoral arterial 'jump' graft of Go[illegible] ped painful red areas on the sole of th[illegible] because of severe

Table III: CONFIGURATIONS AND OU[illegible] [illegible]TERIOVENOUS GRAFTS FOR HAEMODIALYSIS

Graft	No.	Configuration	Primary failure	Range of patency (mth)	Mean patency (mth)	Mean no. dialysis sessions
Saphenous vein	4	Loop	2	0–13	4	90
	4	Straight	2	0–8	3	62
HUCVAG	6 leg	Straight	1	1–12·5	6·7	65
Bovine carotid						
Ficin-digested	4 leg	Straight	0	5·5–16·5	12·3	129
Gluteraldehyde-treated	5	Straight	0	2·25–10	6·9	50
Antibiotic-treated	2 arm	Loop	1	1–6·5	3·8	78
	3 leg	Straight	0	1–5·5	3·8	38
Sparks mandril	3 arm	Loop	3	0·3–1	0·5	0
	5 leg	Loop	1	0·3–2	1	6
	3 leg	Straight	1	1–23·5	15·2	246
Gore-Tex	8 arm	Straight	3	0–14	4·4	78
	5 arm	Loop	1	0·3–8·5	3	33
	9 leg	Straight	0	4·5–17	10	89
Vasculour-D	1 arm	Loop	1	0	0	0
	6 leg	Straight	0	2·5–4·5	3·8	31

Table IV: SUCCESSFUL FUNCTION OF ARTERIOVENOUS GRAFTS IN PATIENTS WITH RENAL FAILURE

Graft	Arm		Leg	
	Loop	Straight	Loop	Straight
Saphenous vein	○●●	○○●●	○	—
Bovine carotid				
Ficin-digested	—	—	—	○○○○
Gluteraldehyde-treated	—	○○○	—	○○
Antibiotic-treated	○	—	—	○○
HUCVAG	—	—	—	○○○●●●
Sparks mandril	●●●	—	●	○○●
Gore-Tex	○○●	○○○●● ●●	—	○○○○○○ ○○○
Vasculour-D	●	—	—	○○○○○○

○, Success; ●, failure.

Table V: COMPLICATIONS OF ARTERIOVENOUS GRAFTS LISTING THE NUMBERS OF GRAFTS AFFECTED

			Bovine carotid artery					
	Saphenous vein	HUCVAG	Ficin-digested	Gluteraldehyde-treated	Antibiotic-treated	Sparks mandril	Gore-Tex	Vasculour-D
No. of grafts	8	6	4	5	5	11	22	7
Thrombectomy	0	3	1	1	0	5	9	0
DVT	0	0	0	0	0	1	1	0
Venous outflow	0	1	3	0	0	0	1	0
Embolism	0	0	0	0	0	0	1	0
Arterial 'steal'	0	0	1	0	0	0	0	0
Bleeding	0	1	2	0	0	1	1	0
Haematoma	0	0	0	0	0	1	0	0
Sepsis	0	1	0	0	0	1	4	0
Aneurysm	0	2	1	0	0	0	0	0

bleeding from cannulation sites, excision of the graft was required.

Arterial 'steal': One patient with a HUCVAG, with obliterated ankle vessels, subsequently experienced severe ischaemia of the foot, presumably brought on by an arterial 'steal' phenomenon. A below-knee amputation was performed.

Bleeding: Secondary haemorrhage from a graft is a very serious problem, because 4 thigh grafts complicated in this manner (HUCVAG, bovine Artegraft, Sparks mandril and Gore-Tex) had to be excised. One further patient with a bovine Artegraft suffered a fatal exsanguinating haemorrhage.

Sepsis: Sepsis along the track of the graft was ineradicable, and 1 thigh Sparks mandril graft and 2 thigh Gore-Tex grafts had to be excised.

Aneurysm formation: Four bioprostheses (3 HUCVAG and 1 bovine Artegraft) developed multiple aneurysms and the grafts were removed thereafter.

Discussion

In end-stage renal failure, when repeated first-stage procedures such as the Scribner shunt or Cimino–Brescia fistula have failed to accomplish vascular access and early kidney transplantation is unfeasible, then second-stage procedures are employed to permit continued dialysis. These may include interposed grafts between suitable artery and vein; translocation of the superficial femoral artery to a subcutaneous position (Brittinger et al., 1970); brachial or proximal radial artery–cephalic vein fistula (Cascardo et al., 1970); and femoral vein and artery catheterization by the Seldinger technique (Shaldon et al., 1961). Larger arteriovenous shunts are now available, such as the Thomas shunt or large vessel appliqué (Thomas, 1970) and the Allen–Brown shunt (Extracorporeal Medical Specialties Incorporated).

With the rapid development of new biological and synthetic graft materials for vascular replacement, not surprisingly, the implantation of a subcutaneous arteriovenous graft has proved to be a popular method of achieving vascular access. Considering first the biological grafts, haemodialysis through autogenous saphenous vein loops in the forearm was first introduced by May and colleagues in 1969. A failure rate of 20–25 per cent in the first 3 months of implantation has been observed, while only 50 per cent of grafts remain patent by 1 year (Foran et al., 1975). Although individual grafts may function for nearly 4 years (Zerbino et al., 1974), many wide-bore vein grafts eventually fail due to intimal fibrosis and aneurysmal dilatation (Foran et al., 1975).

Although the bovine carotid artery graft was originally developed for arterial bypass surgery (Rosenberg et al., 1966), Chinitz and co-workers (1972) were the first to use the xenograft as an arteriovenous conduit to facilitate haemodialysis. The graft is prepared by digesting the adventitia and elastica proteins with ficin, a protease found in fig juice. The remaining collagenous structure is not only strengthened by tanning with dialdehyde starch, but is also rendered essentially non-antigenic. A 1-year patency rate of about 70 per cent is reported (Foran et al., 1975; Rolley et al., 1976), but there is a striking prevalence of needle site infection, bleeding episodes, aneurysms and poor salvageability. Because of a low patency rate of 42 per cent, a sepsis rate of 7 per cent and an aneurysm incidence of 5 per cent, Dale and Lewis (1976) have abandoned using the xenograft for arterial reconstruction. The mean patency rate of some 12 months for the grafts in the present study is in keeping with the other series, but serious complications such as aneurysm formation, massive bleeding and venous outflow problems have made further use of the Artegraft impracticable in this centre.

There has been a sustained interest in the preservation of vascular tissue using two main methods: gluteraldehyde treatment and antibiotic treatment. For instance, the Hancock 'stabilized gluteraldehyde-process-treated' porcine aortic valve (Bowman et al., 1973) has been implanted in many patients with successful function for up to 6 years (Dexter, 1977), and such valves are now available commercially (Edwards Labs). Several investigators have evaluated fresh homograft aortic valves treated with antibiotic cocktails, and these valves have also enjoyed a favourable outcome (Angell et al., 1973). Preservation of bovine carotid arteries collected from the local slaughterhouse is based on the long term studies of Dexter at the Yorkshire Regional Tissue Bank, Wakefield. Despite its shorter shelf-life, the antibiotic-treated graft is preferred to the gluteraldehyde-treated artery because it is more compliant, softer and easier to handle.

Preparation of the HUCVAG is broadly similar to that of the Surgikos Artegraft, whereby, following dilatation of the central umbilical vein, the Wharton's jelly component of the cord is strengthened by tanning either with dialdehyde starch (Mindich et al., 1977) or with gluteraldehyde (Dardik et al., 1976). [illegible] by the two latter groups of the outcome of these homografts are not persuasive, as they give an early thrombosis rate of 40–74 per cent, accompanied by a salvage rate of only 50 per cent. These two factors, in addition to the high cost of the graft and the risk of aneurysm formation, have led to suspension of further implantation in this centre.

In meeting the challenge to provide vascular access in a problem patient, synthetic grafts provide creditable alternatives to the biological grafts. One example, the Sparks mandril, consisting of two layers of knitted Dacron tubing surrounding a flexible inner rod, is buried subcutaneously (Sparks, 1972). When the inner rod is withdrawn after a minimum period of 6 weeks, ingrowth of fibrous tissue has converted the mandril into a vascular prosthesis. Although initially the concept appeared attractive, interest in the mandril has now waned, because of the long maturation period and the incidence of graft closure and aneurysm (Hallin and Sweetman, 1976). The present study confirms their finding that successful long term function can be achieved, provided that the Sparks mandril is anastomosed to wide-calibre vessels.

Early evaluation of expanded reinforced microporous PTFE (Gore-Tex) has shown a patency rate of 86 per cent for over 400 grafts implanted for haemodialysis (Gore Associates Inc., 1977). In the present study, only one thigh graft remained irretrievably closed, probably because of an atheromatous femoral artery. Arteriovenous fistulas and grafts are prone to thrombose if hypotension is incurred after a dialysis session. Thrombectomy is most easily carried out in a Gore-Tex graft, and it is followed by long term patency, provided the inflow and outflow of blood is adequate. Because these requisites were deficient in the arm grafts, salvage attempts here were of little avail.

Dacron velour (Vasculour-D) grafts are warp-knitted from texturized yarn to give loops perpendicular to the flow surface, similar to velvet, producing a fabric of intermediate porosity. These characteristics promote fibrous tissue ingrowth, a well-formed neo-intima and excellent rates of patency in arteriovenous grafts (Flores et al., 1973; Lindenauer et al., 1974). Regarding the three types of synthetic graft, although the Sparks mandril is by far the cheaper, Gore-Tex and Vasculour-D do not require a prolonged maturation period after implantation and also both have received more favourable reports.

In conclusion, conspicuous factors emerge following consideration of the outcome of these 68 arteriovenous grafts for haemodialysis. The first outstanding fact is that a graft placed in straight configuration has a better outcome than a looped graft. The second feature is that a graft located in the thigh enjoys greater success than one in the arm. In general, the patients preferred the thigh location because both hands were then freed for cannulation manoeuvres. Finally, the synthetic grafts incurred less serious complications than the commercial bioprostheses currently available.

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References

ANGELL W. W., WUERFLEIN R. D., CHUN C. W. et al. (1973) Antibiotic sterilisation of aortic homografts. *NZ Med. J.* **77**, 31–35.

BOWMAN F. O., HANCOCK W. D. and MALM J. R. (1973) A valve-containing Dacron prosthesis. *Arch. Surg.* **107**, 724–728.

BRESCIA M. J., CIMINO J. E., APPEL K. et al. (1966) Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *N. Engl. J. Med.* **275**, 1089–1092.

BRITT[illegible]ER W. D., STRANCH M., HUBER W. et al. (1970) 16 months e[illegible]ience with the subcutaneously fixed superficial fe[illegible]l artery for chronic haemodialysis. *Proc. Eur. Tr[illegible] Dial. Assoc.* 7, 408–412.

CASCARI[illegible] ACCHIARDO S., BEVEN E. G. et al. (1970) Proximal arte[illegible]us fistulae for haemodialysis when radial arteri[illegible]navailable. *Proc. Eur. Trans. Dial. Assoc.* **7**, 42–46.

CHINITZ J. [illegible]A T., BOWER R. et al. (1972) Self-sealing prosthe[illegible] a[illegible]riovenous fistula in man. *Tr[illegible] Am. Soc. Artif.* [illegible]*rn. Organs* **18**, 452–455.

DALE W. A. and [illegible]IS M. R. (1976) Further experiences with bovine arterial grafts. *Surgery* **80**, 711–721.

DARDIK H., IBRAHIM I. M., SPRAYREGEN S. et al. (1976) Clinical experience with modified human umbilical cord vein for arterial bypass. *Surgery* **79**, 618–624.

DEXTER F. (1977) Personal communication.

FLORES L., DUNN I., FRUMKIN E. et al. (1973) Dacron arteriovenous shunts for vascular access in hemodialysis. *Trans. Am. Soc. Artif. Intern. Organs* **19**, 33–37.

FORAN R. F., SHORE E. H., LEVIN P. M. et al. (1975) Bovine heterografts for hemodialysis. *West J. Med.* **123**, 269–274.

GORE ASSOCIATES INC. (1977) *Summary of Clinical Evaluation Data for Gore-Tex Vascular Grafts.*

HALLIN R. W. and SWEETMAN W. R. (1976) The Sparks mandril graft. A seven-year follow-up of mandril grafts placed by Charles H. Sparks and his associates. *Am. J. Surg.* **132**, 221–222.

LINDENAUER S. M., WEBER T. R., MILLER T. A. et al. (197[illegible]) Velour vascular prostheses. *Trans. Am. Soc. Artif. Intern. Organs* **20**, 314–318.

MAY J., TILLER D., JOHNSON J. et al. (1969) Saphenous vein arteriovenous fistula in regular dialysis treatment. *N. Engl. J. Med.* **280**, 770–771.

MINDICH B., SILVERMAN M., ELGUEZABEL A. et al. (1977) Human umbilical cord vein for vascular replacement: preliminary report and observations. *Surgery* **81**, 152–160.

QUINTON W. E., DILLARD D. H. and SCRIBNER B. H. (1960) Cannulation of blood vessels for prolonged hemodialysis. *Trans. Am. Soc. Artif. Intern. Organs* **6**, 104–113.

ROLLEY R. T., STERIOFF S. and WILLIAMS G. M. (1976) Arteriovenous fistulas for dialysis using modified bovine arteries. *Surg. Gynecol. Obstet.* **142**, 700–704.

ROSENBERG N., MARTINEZ A., SAWYER P. N. et al. (1966) Tanned collagen arterial prosthesis of bovine carotid origin in man. *Ann. Surg.* **164**, 247–256.

SHALDON S., CHIANDUSSI L. and HIGGS B. (1961) Haemodialysis by percutaneous catheterisation of the femoral artery and vein with regional heparinisation. *Lancet* **2**, 857–859.

SPARKS C. H. (1972) Silicone mandril method of femoropopliteal artery bypass. *Am. J. Surg.* **124**, 244–249.

THOMAS G. I. (1970) Large vessel appliqué arteriovenous shunt for hemodialysis. A new concept. *Am. J. Surg.* **120**, 244–248.

ZERBINO V. R., TICE D. A., KATZ L. A. et al. (1974) A 6-year clinical experience with arteriovenous fistulas and bypasses for hemodialysis. *Surgery* **76**, 1018–1023.

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Neurofibrosarcoma of the duodenum in von Recklinghausen's disease

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SUMMARY

The clinical features and surgical management of 2 patients with neurofibrosarcoma of the duodenum in association with von Recklinghausen's disease are described. The tumours were excised and the resulting duodenal defects closed satisfactorily using the jejunal serosal patch technique. Three such neurofibrosarcomas reported previously in English are reviewed.

NEUROFIBROMA and neurofibrosarcoma of the small bowel account for 2·4 per cent and 0·6 per cent respectively of small bowel tumours (Sivak et al., 1975). Over 80 per cent of enteric neurofibromas occur without cutaneous neurofibromatosis (River et al., 1956), but 11 per cent of patients with von Recklinghausen's disease develop such tumours (Das Gupta, 1969). The incidence of sarcomatous degeneration of neurofibromas in patients with von Recklinghausen's disease rises with age and length of follow-up. It has been reported to range from 4·4 per cent (Knight et al., 1973) to 66 per cent (Das Gupta, 1969). Malignant change in small bowel neurofibromas has rarely been reported. We were able to find details of only 14 cases reported previously: 6 neurofibrosarcomas were in the duodenum and of these, 3 were in patients with von Recklinghausen's disease. We present 2 further cases with emphasis on the clinical presentation and surgical management.

Case reports

Case 1: A 64-year-old woman with von Recklinghausen's disease and a 24-h history of severe right-sided upper abdominal pain and two episodes of haematemesis was admitted as a surgical emergency. On examination, she had generalized peritonitis and a diffuse mass was palpable in the right upper quadrant. At laparotomy, the antimesenteric border of the entire small bowel was studded with many small neurofibromas. On the anterior wall of the second part of the duodenum was a large necrotic tumour which had perforated the duodenum and also invaded the hepatic flexure of the colon. The duodenal tumour was excised and a right hemicolectomy performed. The defect in the anterior duodenal wall, which was 4×3 cm in diameter, was repaired using a loop of proximal jejunum, brought through the mesocolon and sutured to the free edge of the duodenal defect as a serosal patch. The operation was completed with a proximal jejunojejunostomy to divert intestinal contents from the region of the duodenal repair.

The patient's condition remained poor. On the fifth post-operative day she developed bilateral ileofemoral thrombosis and pulmonary embolism and died 5 days later. Post-mortem examination showed that death was due to bronchopneumonia and multiple pulmonary emboli. Histology of the tumour (*Fig.* 1) showed it to be a neurofibrosarcoma infiltrating the hepatic flexure of the colon.

Case 2: A 34-year-old male Pakistani with von Recklinghausen's disease was admitted as an emergency with a 48-h history of central and right-sided abdominal pain and bilious vomiting. On examination, his abdomen was tense, with rebound tenderness over a diffuse mass to the right of the umbilicus. Bowel sounds were normal. At laparotomy a large lobulated tumour arising from the anterior aspect of the second part of the duodenum projected through the mesocolon. There were also multiple neurofibromas studded along the antimesenteric border of the jejunum. The tumour was mobilized and resected leaving a defect of 5×3 cm in the anterior duodenal wall. This was repaired, as in the first case, by a jejunal serosal patch. As the tumour had infiltrated the mesocolon and compromised the circulation to the ascending colon, a hemicolectomy was also performed. The patient remains well 2 years later.

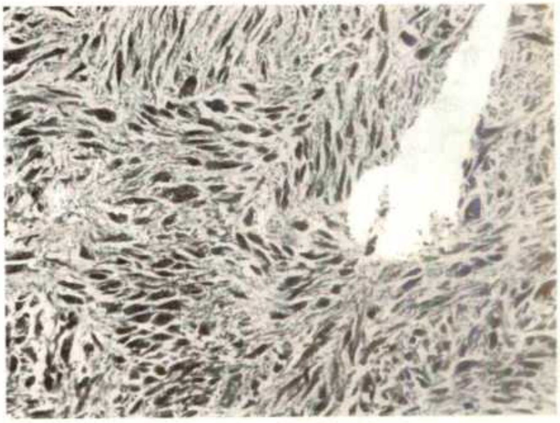

Fig. 1. *Case* 1. Photomicrograph of duodenal neurofibrosarcoma. (HE. × 225.)

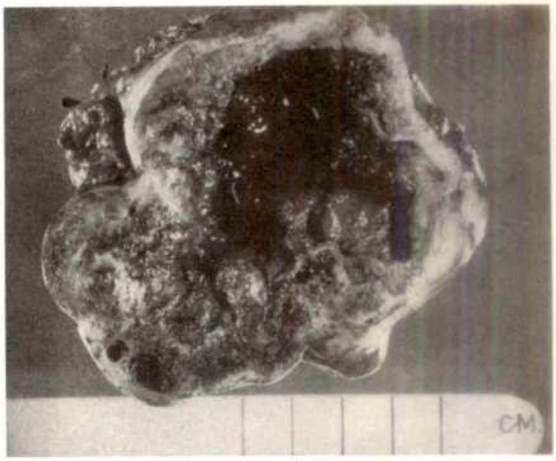

Fig. 2. *Case* 2. Duodenal neurofibrosarcoma, showing necrotic haemorrhagic central cavity.

The resected tumour was 8 cm in diameter with central necrosis and recent haemorrhage (*Fig.* 2). Histologically it was a neurofibrosarcoma which had penetrated the duodenal wall.

Discussion

Most intestinal neurofibromas are asymptomatic and are incidental findings at laparotomy or at post-mortem (Nilsson and Jonsson, 1957). They can, however, cause abdominal discomfort, melaena or obscure anaemia (River et al., 1956) and the diagnosis

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of intestinal neurofibromatosis should be considered whenever a patient with von Recklinghausen's disease develops such symptoms. In cases reported in the literature there is an average delay of about 3 years before the diagnosis is made (Sivak et al., 1975). A high index of suspicion, thorough radiological and endoscopic investigation and willingness to perform early laparotomy may prevent life-threatening complications such as malignant degeneration or massive gastrointestinal bleeding.

Neurofibrosarcomas probably arise from malignant degeneration of pre-existing neurofibromas in the autonomic plexuses of the bowel wall. These tumours are very vascular, and, as they grow, the centre tends to become haemorrhagic and necrotic. Bleeding into the centre of the tumour probably caused the pain with which our second patient presented. Continued tumour growth may result in mucosal infiltration, with ulceration and haemorrhage into the gut. As a result of mucosal erosion the necrotic central part of the tumour may be exposed to the intestinal contents, and become infected (Cedermark, 1949). The tumour may also ulcerate through the peritoneal surface of the duodenum causing perforation and peritonitis, as in our first patient.

Three cases of duodenal neurofibrosarcoma in association with von Recklinghausen's disease have been previously reported (Russell, 1965; Beaven and Donovon, 1970; Clapp and Haas, 1971). All three patients had past histories of abdominal pain, melaena or anaemia, which had been investigated without a definite diagnosis being made. Each of these patients subsequently presented as a surgical emergency. Two of the patients had developed intra-abdominal sepsis owing to erosion of the tumour through the duodenal wall, and both died soon after operation. The third patient presented with massive intestinal haemorrhage. This patient survived resection of the tumour but a long term follow-up was not reported.

Three patients with duodenal neurofibrosarcomas in the absence of cutaneous neurofibromatosis have been reported previously (Cedermark, 1949; Elliot and Hansson, 1951; Nilsson and Jonsson, 1957). In two of these patients the presenting symptoms were dyspepsia and melaena and a radiological diagnosis of duodenal tumour was made on barium meal examination. In the third patient, results of barium meal examination were normal and the diagnosis was made at laparotomy. In 2 cases the tumours were not resectable and the patients died with metastases 3 years and 18 months respectively after operation. In the third patient a small tumour was excised but no long term follow-up was reported.

Resection of duodenal lesions is complicated by the difficulty of closing the resulting defect. The serosal patch technique is a relatively simple procedure and has been used successfully to close duodenal fistulas after gastroduodenal surgery (Jones et al., 1973) and allows resection of colonic tumours involving the duodenum (Ellis et al., 1972). We believe that with the use of the jejunal serosal patch to close the duodenal defect, large tumours of the second part of the duodenum can be successfully resected even under emergency conditions.

References

BEAVEN W. E. and DONOVAN D. C. (1970) Lower gastrointestinal hemorrhage secondary to enteric neurofibromatosis (Recklinghausen's disease). *N Y State J. Med.* **70**, 2677–2681.

CEDERMARK J. (1949) Neurinoma in the gastro-intestinal tract. *Acta Chir. Scand.* **97**, 473–484.

CLAPP W. A. and HAAS R. (1971) Neurofibrosarcoma of the duodenum. *J. Maine Med. Assoc.* **62**, 55–56.

DAS GUPTA T. K. (1969) Multiple neurofibromatosis (von Recklinghausen's disease). *Proc. Inst. Med. Chic.* **27**, 254–255.

ELLIOT A. and HANSSON C. J. (1951) Neurosarcoma duodeni. *Acta Radiologica* **35**, 407–412.

ELLIS H., NAUNTON MORGAN M. and WASTELL C. (1972) 'Curative' surgery in carcinoma of the colon involving duodenum: a report of 6 cases. *Br. J. Surg.* **59**, 932–935.

JONES S. A., GAZZANIGA A. B. and KELLER T. B. (1973) The serosal patch: a surgical parachute. *Am. J. Surg.* **126**, 186–196.

KNIGHT W. A., MURPHY W. K. and GOTTLIEB J. A. (1973) Neurofibromatosis associated with malignant neurofibromas. *Arch. Dermatol.* **107**, 747–750.

NILSSON B. and JONSSON I. (1957) Malignant neurinoma of the duodenum: report of one case and review of the literature. *Acta Chir. Scand.* **113**, 357–363.

RIVER L., SILVERSTEIN J. and TOPE J. W. (1956) Benign neoplasms of the small intestine: a critical comprehensive review, with reports of 20 new cases. *Int. Abstr. Surg.* **102**, 1–38.

RUSSELL J. Y. W. (1965) Neurofibromatosis: a bizarre disease. *Br. J. Surg.* **52**, 251–262.

SIVAK M. V., SULLIVAN B. H. and FARMER R. G. (1975) Neurogenic tumours of the small intestine: review of the literature and report of a case with endoscopic removal. *Gastroenterology* **68**, 374–380.

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Pyeloduodenal fistula: a case report and review of the literature

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SUMMARY

A case of the rare condition of pyeloduodenal fistul presented—the thirty-second case so far recorded in literature. The authors consider that this instance s some of the features typical of the cases so far rep ed.

The literature is reviewed and the aetiology, presentation, diagnostic methods and treatment are briefly discussed.

FISTULOUS connection between the renal and alimentary tracts is itself unusual and spontaneous pyeloduodenal fistula is one of the rarer types. In exhaustive review Abeshouse (1949) found or cases of pyeloduodenal fistula in a total of 277 alimentary fistulas of all types. W 31 reported cases (*Table I*) and case, due to chronic pyonephro

Case report

A 44-year-old man with fever, general mala anorexia. After 10 right loin pain, dysuria, urinary symptoms settled after a fever and malaise continued. Ten da ed to hospital for investigation.

Further questioning revealed a 4-year history of recurrent febrile illnesses, each similar to his current attack, but there was no past history of urinary disorder.

On admission he had a fever of 39 °C and a tender mass in the right loin. Investigations showed a haemoglobin of 11·4 g/dl and a WBC of 17·3 × 10⁹/l. Biochemistry was normal, MSU contained red cells but no growth and an intravenous pyelogram showed a normal left renal tract but a non-functioning right kidney.

Four days after admission the patient's temperature suddenly fell to normal with a dramatic improvement in his general condition unassociated with any new symptoms. Cystoscopy the same day revealed no abnormality. A retrograde pyelogram of the right side revealed a grossly distorted pelvicalyceal system and free flow of contrast medium into the duodenum (*Fig.* 1).

Renal puncture was then performed under X-ray control: 80 ml of pus were aspirated and contrast studies confirmed the changes in the right kidney (*Fig.* 2). Culture of the pus yielded a heavy growth of *Escherichia coli* and the patient was started on a course of cephradine. He was discharged home feeling well on the seventh day.

Two weeks later a further intravenous pyelogram showed a thin shell of renal tissue with large cystic spaces on the right but no clear outline of the pelvicalyceal system or ureter. Contrast medium was seen in the small bowel on later films.

Although symptom-free the patient was readmitted 4 weeks after discharge from hospital for exploration of the right kidney. The kidney was approached posteriorly and dense fibrosis was encountered around it, especially at the hilum, where a fistulous connection was found between the dilated renal pelvis and the posterior aspect of the duodenum (*Fig.* 3). Nephrectomy was performed, dividing the fistula and repairing the duodenal defect. The patient's postoperative recovery was uneventful and he was discharged home on the tenth day.

Macroscopically, the specimen revealed a grossly dilated pelvicalyceal system lined with blood clot and exudate surrounded by a thin shell of kidney tissue. The microscopic appearances were those of chronic pyonephrosis.

iscussion

Cases of pyeloduodenal fistula have been divided into traumatic and spontaneous, no case of congenital fistula ever having been reported. With one exception, all the reported cases involved the right kidney. Arendt and Brockman (1934) reported a case involving the left kidney and the terminal duodenum.

Traumatic fistulas form the smalle group, but since 1945 these appear to be incr asin n requency (Bissada et a . 19). Reporte ha been due to b llet wo Dougal a ky, 972; Bissada penetrati denum by ingested dies (Abe 49; Schimmel, 1971), injuries (I o; Arthur and Morris,), surgica on of the renal tract eshou al., 1961) and drainage of suppo ts (the hydronephrotic renal num (Morson and Stiddolph, l., 1973). Trauma may lead to ood or urine into the perinephric nric abscess and eventual rupture into um (Abeshouse, 1949). This process is spontaneous fistula formation in the nce of chronic renal inflammatory disease. Probably some cases of spontaneous fistula are preceded by an episode of trauma, the diseased renal pelvis being more likely to rupture.

Generally, spontaneous pyeloduodenal fistula results from a pathological process in the kidney. Only one case due to duodenal pathology is reported (von Friedman and Lefke, 1969), although Hoare (1973) reports a case of ureteroduodenal fistula ascribed to a duodenal ulcer. Tuberculosis was considered to be an important cause; there are, however, only 5 reported cases in the literature (*Table I*).

Chronic renal inflammatory disease accounts for the majority of cases. Of the 31 cases we have collected 23 were due to chronic infection. Fifteen of these were associated with calculus and 10 also had a perinephric abscess. Urinary obstruction appears to be important in the pathogenesis, leading to extensive perinephritis and eventual rupture into adjacent organs (Abeshouse, 1949; Arthur and Morris, 1966). An obstructing calculus may erode through into the duodenum (Pulvertaft, 1935; McEwan, 1968). Bissada et al. (1973) have found a striking increase in the incidence of associated calculus since 1945 and suggest that, since the advent of effective chemotherapy, an obstructive element is necessary in addition to virulent infection.

We consider our case to be one of chronic pyonephrosis, the pelvicalyceal system being grossly dilated with only a thin shell of renal tissue. There was no evidence of suppuration in the perinephric space and the renal pelvis was in direct apposition

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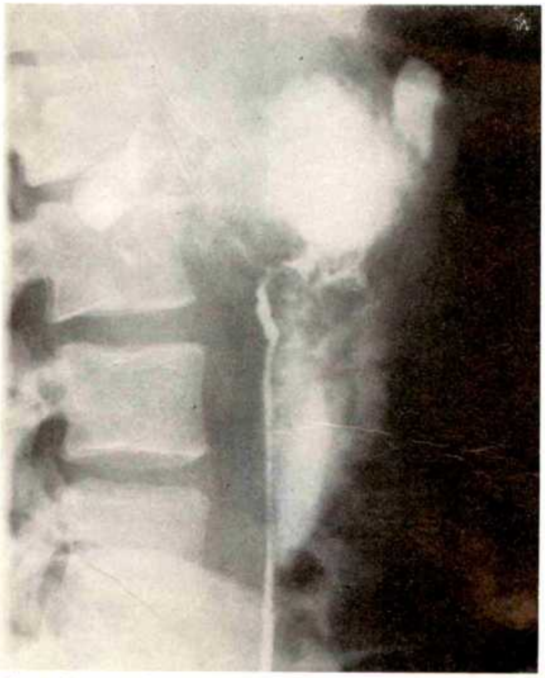


Fig. 1. Retrograde pyelogram (lateral view) showing the pelvicalyceal system and duodenum.

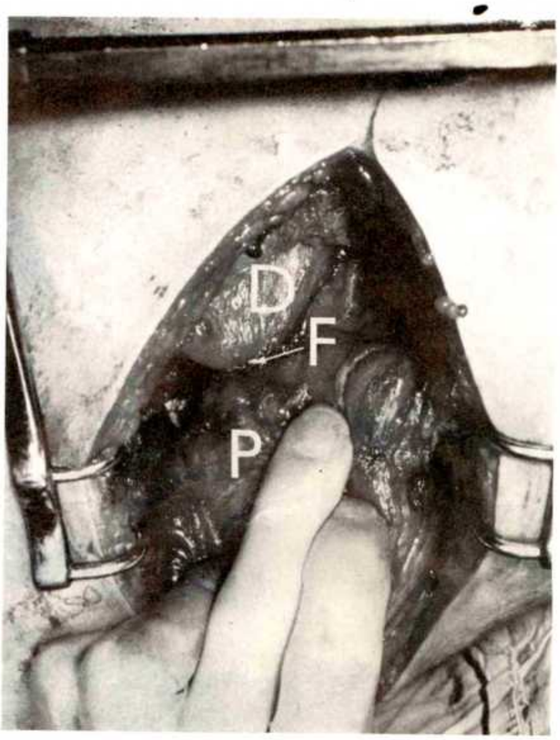


Fig. 3. The right kidney has been exposed through a loin incision and is being drawn down. The fistulous connection (F) between the duodenum (D) and the renal pelvis (P) can be clearly seen.

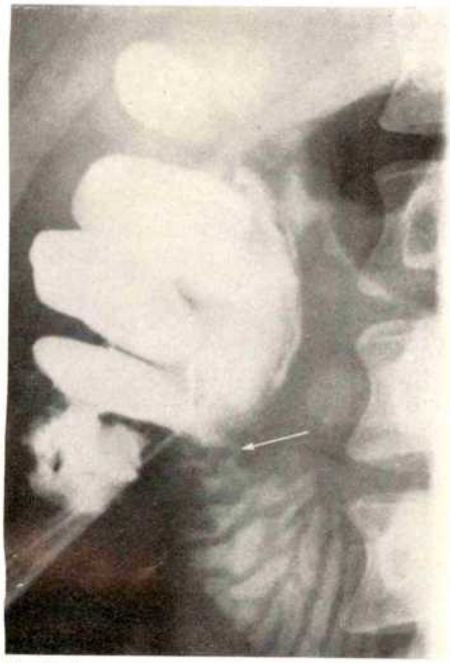


Fig. 2. Percutaneous renal puncture showing cannula in the renal pelvis. The pelvicalyceal system is clearly outlined, and the fistulous track (arrowed) can be seen. There is no flow of contrast medium down the right ureter.

with the duodenum (*Fig.* 3). It is interesting to note that no calculus was found though there was evidence of obstruction at the pelviureteric junction.

Although a few cases present with symptoms of renal disease, the commonest modes of presentation are diarrhoea, vomiting, epigastric pain and weight loss. The reflux of pus or urine into the duodenum may cause these symptoms. There have been two cases of metabolic disorder as a result of urinary reabsorption from the bowel (Boggs et al., 1961; Bissada et al., 1973). Occasionally the fistula may be entirely silent. In our case there was a past history of recurrent 'flu-like illnesses. Only the final attack brought transient symptoms and signs of pyelonephritis which prompted admission. It is uncertain when the fistulous connection with the duodenum was established. The patient showed sudden improvement on the fourth day of his first admission and this event probably signified spontaneous drainage into the duodenum.

The precise diagnosis of pyeloduodenal fistula relies on radiological investigation. The intravenous pyelogram usually shows, as in this case, a non-functioning kidney. There was no suggestion of fistula on the first IVP but after spontaneous decompression the second IVP 3 weeks later showed a poor nephrogram and contrast medium in the bowel in late films. The diagnosis is usually established by retrograde pyelography. In cases with obstruction of the ureter the fistula may be outlined by upper gastro-intestinal barium studies (Schwartz et al., 1970; Geisse and Blath, 1976). Fistulas have been shown by

Table I: SUMMARY OF PREVIOUSLY REPORTED CASES OF SPONTANEOUS PYELODUODENAL FISTULA

Author	Aetiology	Operation	Outcome
Campaignac, 1839	Pyelonephritis, perinephric abscess, calculus	None	Died
Barlow and Rees, 1843	Renal hydatid disease	None	Died
Hinton, 1866	Previous trauma with cutaneous fistula, perinephric abscess calculus	None	Died
Bang, 1874	Tuberculous hydronephrosis	None	Died
Turner, 1893	Tuberculous perinephric abscess	None	Died
Esau, 1911	Perinephric abscess	None	Died
Terebinskiy, 1929	Pyelonephritis, perinephric abscess, calculus	Yes	Died
Arendt and Brockman, 1934	Pyelonephritis, perinephric abscess and calculus	Yes	Died
Biondi, 1935	Renal tuberculosis	Fistulectomy then nephrectomy	Satisfactory
Pulvertaft, 1935	Chronic pyelonephritis, calculus (considered by others to be TB)	Drainage of abscess	Died
Ribiero, 1939	Pyelonephritis, perinephric abscess	Yes	Died
King, 1950	Pyelonephritis (silent)	Nephrectomy	Satisfactory
Jones et al., 1953	Renal epidermoid carcinoma, calculus	Exploration	Died
Bloom, 1954	Pyelonephritis, calculus	Nephrectomy	Satisfactory
Glaser, 1954	Pyelonephritis, calculus	Yes	Died
Barootes, 1956	Pyelonephritis, calculus	Nephrectomy	Satisfactory
North et al., 1956	Pyelonephritis, calculus	Nephrectomy	Satisfactory
Boggs et al., 1961	Pyonephrosis (retrograde pyelography 6 weeks before)	Nephrostomy, fistulectomy. Nephrectomy	Satisfactory
Boggs et al., 1961	Pyelonephritis, calculus	Nephrectomy	Satisfactory
Pumphrey, 1963	Pyelonephritis, perinephric abscess, calculus	Nephrectomy	Satisfactory
Arthur and Morris, 1966	Perinephric abscess, pyelonephritis, calculus (following a fall 9 yr previously)	Nephrectomy	Satisfactory
Cohen et al., 1966	Pyelonephritis, perinephric abscess. Renal papillary carcinoma	Exploration	Satisfactory
Hopkins and Pierce, 1966	Perinephric abscess, pyelonephritis, calculus	Nephrectomy	Satisfactory
Newsam, 1966	Pyelonephritis	Nephrectomy	Satisfactory
Wise and Schimada, 1967	Tuberculosis	Nephrectomy	Satisfactory
McEwan, 1968	Chronic pyelonephritis and calculus, discharging nephrostomy sinus	None	Well
von Friedmann and Lefke, 1969	Atypical duodenal diverticulum	Nephrectomy	Satisfactory
Schwarz et al., 1970	Pyelonephritis	Nephrectomy	Satisfactory
Bissada et al., 1973	Pyonephrosis, perinephric abscess and calculus	None	Died
Geisse and Blath, 1976	Chronic pyelonephritis	Nephrectomy	Satisfactory
Geisse and Blath, 1976	Chronic pyelonephritis and calculus	Nephrectomy	Satisfactory

micturating cystography (Bissada et al., 1973) and by identifying air in the pelvicalyceal system (Cohen et al., 1966).

The treatment of choice is surgical, nephrectomy with closure of the duodenal defect being the commonest procedure. Some authors consider surgery mandatory, but McEwan (1968) has pointed out that those patients dying whilst on conservative management probably succumb from general effects of their disease rather than from local effects of the fistula. Nevertheless, almost all cases since 1935 have undergone surgery with only two deaths (*Table I*).

Our case remained symptom-free after apparent spontaneous decompression of the kidney and treatment with antibiotics, and nephrectomy was deferred without complication. Operation was undertaken because it seemed unlikely that conservative management would cure the disease and it was impossible to exclude malignant disease without exploration.

References

ABESHOUSE B. S. (1949) Renal and ureteral fistula of the visceral and cutaneous types: a report of 4 cases. *Urol. Cutan. Rev.* **53**, 641–674.

ARENDT J. and BROCKMAN H. (1934) Ungewöhnliche pyelographische Befunde. *Fortschr. Geb. Roentgenstr.* **49**, 335–341.

ARTHUR G. W. and MORRIS, D. G. (1966) Reno-alimentary fistulae. *Br. J. Surg.* **53**, 396–402.

BANG B. F. L. (1874) Primae tuberculose i urogenitalorganerne; kommunikation immellern duodenum og den hojere ureter. *Hosp. Tid Kjobenh.* **1**, 561–565.

BARLOW G. H. and REES G. D. (1843) Account of observations on patients whose urine was albuminous. *Guys Hosp. Rep.* **1**, 189.

BAROOTES E. W. (1956) Spontaneous pyeloduodenal fistula. *J. Int. Coll. Surg.* **26**, 540–546.

BIONDI C. G. (1935) Duodenorenal fistula. *JAMA* **104**, 1894–1897.

BISSADA N. K., COLE A. T. and FRIED F. A. (1973) Reno-alimentary fistula: an unusual urological problem. *J. Urol.* **110**, 273–276.

BLOOM B. (1954) Spontaneous renoduodenal fistulas. *J. Urol.* **72**, 1153–1158.

BOGGS J. E., BLUNDON K. E. and DAVIS D. M. (1961) Pyeloduodenal fistula. *J. Urol.* **86**, 199–204.

CAMPAIGNAC (1839) Cited by RAYER P. (1839) *Traité des Maladies des Reins.* Paris, Baillière, vol. 3, p. 293.

COHEN M. H., BECKER M. H. and HOTCHKISS R. S. (1966) Pyeloduodenal fistula: report of a case and review of the literature. *J. Urol.* **95**, 678–680.

ESAU J. (1911) Subcutane Zerreibung der rechten Niere mit Abscedienung und Duodenal fistel Bildung. *Med. Klin.* **7**, 1538–1540.

GEISSE G. and BLATH R. A. (1976) Spontaneous nephroduodenal fistula. *J. Can. Assoc. Radiol.* **27**, 118–121.

GLASER S. (1954) Nephroduodenal fistula. *Br. J. Urol.* **26**, 261–263.

HINTON J. (1866) Case of renal calculus. *Br. Med. J.* **1**, 122.

HOARE E. M. (1973) Duodenoureteric fistula. *Br. J. Surg.* **60**, 407–410.

HOPKINS W. F. and PIERCE J. M. jun. (1966) Spontaneous pyeloduodenal fistula: a case report. *J. Urol.* **95**, 489–492.

JONES G. H., MELENDY O. A. and FLYNN W. F. (1953) Spontaneous nephroduodenal fistula: review of the literature and report of one case. *J. Urol.* **69**, 760–763.

KING J. D. (1950) Spontaneous renoduodenal fistulas. *Radiology* **54**, 82–85.

MCDOUGAL W. S. and PERSKY L. (1972) Traumatic and spontaneous pyeloduodenal fistulas. *J. Trauma* **12**, 665–669.

MCEWAN A. J. (1968) Pyeloduodenal fistula. *Br. J. Urol.* **40**, 350–353.

MORSON C. and STIDDOLPH N. E. (1951) A case of anastomosis of the duodenum to a hydronephrotic sac. *Br. J. Urol.* **23**, 62–63.

NEWSAM J. E. (1966) A case of nephroduodenal fistula. *Br. J. Urol.* **38**, 492–494.

NORTH J. P., LIVINGSTON S. O. and LOVELL B. K. (1956) Spontaneous renoduodenal fistula. *Surgery* **39**, 683–687.

PULVERTAFT R. J. V. (1935) Duodenorenal fistula. *Lancet* **1**, 24–25.

PUMPHREY J. D. (1963) Pyeloduodenal fistula: a case report. *Ann. Surg.* **158**, 260–262.

RIBIERO E. B. (1939) Sobré um caso singular de lithiase rénal (fistula lombo-bronchica e fistula lombo-enterica). *Ann. Paulist. Med. Cir.* **38**, 215.

SCHIMMEL F. (1971) Fistule duodeno-renale par corps etranger. *J. Urol. Nephrol. (Paris)* **77**, Suppl., pp. 423–429.

SCHWARTZ D. T., GARNES H. A., LATTIMER J. K. et al. (1970) Pyeloduodenal fistula due to tuberculosis. *J. Urol.* **104**, 373–375.

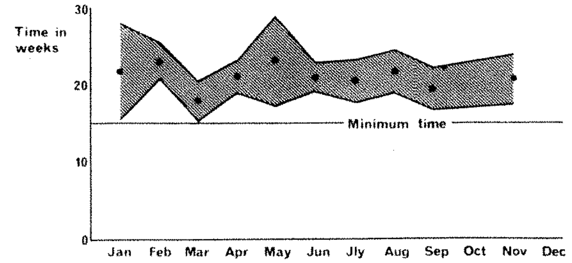
TEREBINSKIY N. N. (1929) Pyeloduodenal fistula. *Russk. Klin.* **12**, 859.

TURNER J. (1893) Cited by PERRY E. C. and SHAW L. E. (1893) On diseases of the duodenum. *Guys Hosp. Rep.* **50**, 305–308.

VON FRIEDMAN G. and LEFKE M. (1969) Röntgenologischer nachweis einer Duodenorenalen fistel. *Fortschr. Geb. Foentgenstrahl* **111**, 821–827.

WISE H. M. and SCHIMADA T. (1967) Pyeloduodenal fistula: a case report. *J. Urol.* **97**, 987–989.

Paper accepted 16 June 1978.



Time from acceptance to publication of articles in the *British Journal of Surgery*.

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The value of corpus–antrum border determinations in highly selective vagotomy

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SUMMARY

In order to know whether the exact determination of the corpus–antrum border is of importance in highly selective vagotomy (HSV) the operation was performed on two matched groups of patients with duodenal ulcers. In group 1 (35 patients) HSV was performed using anatomical landmarks to define the distal extent of dissection. In group 2 (35 patients) HSV was performed using the same technique and then a gastrotomy was made and any remaining acid-secreting mucosa was identified using pH-metry under pentagastrin stimulation. In 22 cases secretion of acid was observed distal to the anatomically defined corpus–antrum border. In these patients a further distal division of vagal branches was done until no acid secretion was observed. Two months and 1 year after the operation, basal acid output (BAO), pentagastrin-stimulated acid output (PAO_{pg}), insulin-stimulated acid output (PAO_I) and basal serum gastrin determinations were done and compared with the corresponding preoperative data. Our results show that despite the more extensive division of the antral vagal branches in group 2, BAO and PAO_{pg} were similar in both groups postoperatively. Postoperative PAO_I was also similar. Differences were observed, however, in postoperative serum gastrin levels—group 1 42·5 ± 6·0 pmol/l and group 2 81·7 ± 7·4 pmol/l 1 year after the operation. In no cases did the more extensive dissection of antral vagal branches lead to clinical or radiological gastric stasis. Thus, if the branches of the nerves of Latarjet are used as landmarks in performing HSV, in many cases vagally innervated, acid-secreting mucosa will be left in the stomach, but apparently this is quantitatively of minor importance. On the other hand, a more extensive distal vagal dissection leads to disturbingly high postoperative serum gastrin values.

In highly selective vagotomy (HSV) the aim is to denervate the acid-secreting part of the stomach—the parietal cell mass. The extent of the distal dissection is usually based on anatomical landmarks; it can also be determined by identification, 'mapping' of the corpus–antrum border using pH-metry (Amdrup and Jensen, 1970). Whether pH-metry is really necessary is still a debatable issue (Goligher, 1974; Johnston, 1975). We have studied this question in two groups of duodenal ulcer patients subjected to highly selective vagotomy without pyloroplasty. In one group the dissection was carried out using the branches of the nerves of Latarjet as anatomical landmarks. In the second group a gastrotomy was made after a dissection based on these landmarks and the corpus–antrum border was identified by pH-metry. This was followed by extended denervation if indicated by the pH values. An assessment was made of the gastric acid secretion and basal serum gastrin values in both groups 1 year after surgery.

Patients and methods

Patients

The series consisted of consecutive patients admitted for elective surgical treatment of chronic duodenal ulcer disease. Altogether 70 patients participated in this study. In group 1 35 patients were subjected to HSV in a hospital in Turku, where the operation was carried out without intragastric mapping of the corpus–antrum border. In group 2 35 patients were subjected to similar surgery in a hospital in Helsinki, where intragastric identification of the corpus–antrum border was performed. The diagnosis of chronic duodenal ulceration was based on clinical, radiological and endoscopic findings and confirmed at operation. The indication for surgery was resistance to conservative treatment in both groups. As shown in *Table I*, the groups were satisfactorily matched with regard to age and sex distribution and preoperative secretion data.

Table I: PREOPERATIVE DATA

Group	F/M	Age (yr mean ± s.e. mean)	Acid secretion (mmol/h; mean ± s.e. mean) BAO	PAO_{pg}	Basal serum gastrin (pmol/l; mean ± s.e. mean)
1	5/30	43·9 ± 2·2	4·2 ± 0·9	39·4 ± 3·1	36·5 ± 3·1
2	8/27	43·5 ± 1·7	4·6 ± 0·7	39·1 ± 2·2	36·4 ± 4·0

F, Female; M, male.

Technique of HSV

The operation was essentially carried out according to the technique of Johnston and Wilkinson (1970). All operations were performed by the authors, who have trained together as surgeons and were originally members of the same vagotomy team. In group 1, where pH-metry was not performed, the distal extent of the dissection was determined by the distribution of the nerves of Latarjet. The end-point of denervation was located where the terminal branches of the nerves passed at right angles into the antral wall, from 6 to 8 cm (mean 7 cm) from the pylorus.

In group 2, in which intragastric mapping was always performed, a similar dissection was first carried out. An anterior gastrotomy was then made proximal to the level of the presumed corpus–antrum border. Premedication and anaesthesia excluded the use of atropine. Pentagastrin infusion (6 μg kg^{-1} h^{-1}) was started 15 min before the gastrotomy was made. Hydrochloric acid in the stomach was neutralized with 1·5 per cent sodium bicarbonate followed by washings with distilled water. The gastric mucosa was painted with Congo Red (red at pH above 5, black at pH below). To locate and delineate eventual areas of low mucosal pH a pH-meter (Radiometer, Copenhagen) was used. In the presence of mucosal areas with low pH the corresponding vagus branches were identified and cut. The washing procedure was repeated and the denervation continued, until no areas with a pH less than 5 could be detected. In 22 of the 35 patients the distal denervation had to be continued for an additional 1–5 cm (mean 2 cm). In these 22 cases the final length of innervated antrum was, on the average, 5 cm. Additional denervation was not required in 13 patients with a mean length of innervated antrum estimated as 7 cm.

Finally, in group 2, the intactness of antral motor nerve supply was assessed using a Burge stimulator (Burge and Vane, 1958). This was placed around both nerves of Latarjet and

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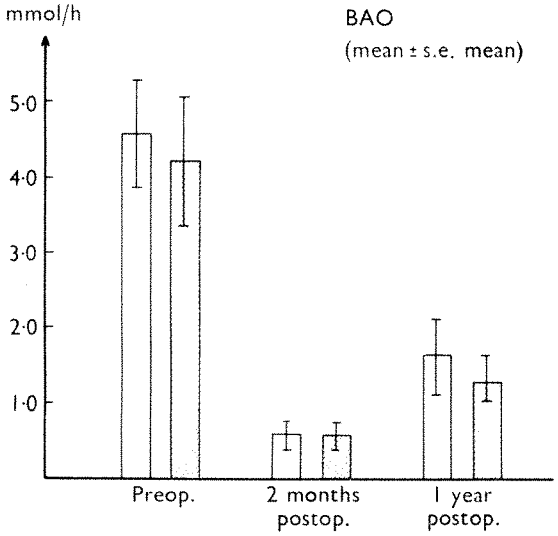


Fig. 1. Effect of highly selective vagotomy on basal gastric acid output (BAO). White, group 1 patients, without mapping of the corpus–antrum border; shaded, group 2 patients, with mapping of the corpus–antrum border. No statistically significant difference existed between the groups at any given point.

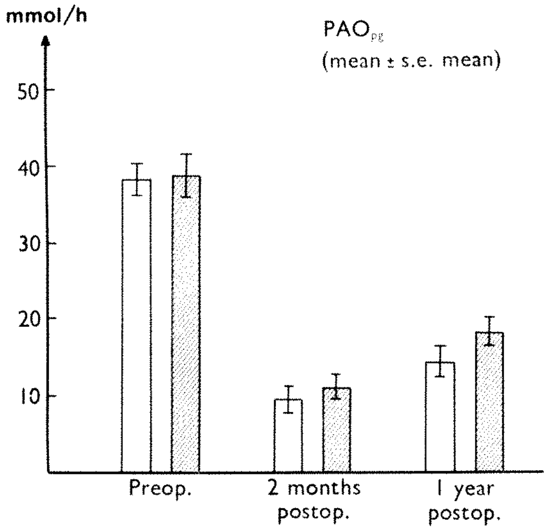


Fig. 2. Effect of highly selective vagotomy on peak acid output stimulated by pentagastrin (PAO$_{pg}$). White, group 1 patients, without mapping of the corpus–antrum border; shaded, group 2 patients, with mapping of the corpus–antrum border. No statistically significant difference existed between the groups at any given point.

around the freed lesser omentum. The antral peristaltic waves resulting from electrical stimulation were observed by direct vision and recorded using a rubber balloon connected to a pressure transducer and electronic recorder.

Measurement of acid secretion before and after HSV
Basal acid output (BAO) and pentagastrin-stimulated peak acid output (PAO$_{pg}$) were determined in all patients preoperatively as described by Baron (1973). An especially designed suction pump was used for collection of gastric secretions (Egnell, Stockholm). The correct location of the radio-opaque nasogastric tube was checked by radiography. For determination of BAO, gastric secretions were collected during four 15-min periods. A pentagastrin dose of 6 μg/kg body weight (Peptavlon, Imperial Chemical Industries, England) was given intramuscularly for determination of PAO$_{pg}$. Four 15-min batches of gastric juice were collected. One-millilitre samples of gastric juice were titrated with 0·01 N NaOH to pH 7 after filtration. PAO$_{pg}$ was calculated from the two highest consecutive periods after stimulation.

At 2 months and at 12 months after HSV, insulin-stimulated peak acid output (PAO$_I$) together with BAO and PAO$_{pg}$ determinations were made. An insulin dose of 0·2 U/kg body weight was given; the test was performed according to Baron (1973). The insulin response was considered positive if the acid concentration in one 15-min sample exceeded the highest basal value by 20 mmol/l or more. In addition to this original Hollander estimation, the criteria of Ross and Kay (1964) were used to distinguish between early and late positivity. PAO$_I$ was calculated from the two highest consecutive periods. BAO was not subtracted from the obtained values. Blood glucose was analysed on an autoanalyser 30 and 45 min after insulin injection using the glucose oxidase method. A decrease of blood glucose concentration to less than 35 mg/100 ml was used as the criterion of adequate insulin stimulation.

Serum gastrin
The blood samples for determination of basal serum gastrin were taken after overnight fasting and without aspiration of the stomach contents. Gastrin concentrations were determined radioimmunochemically (Yalow and Berson, 1970). The antibody used was raised in rabbits against synthetic gastrin-17. The gastrin determinations were performed before and 12 months after HSV.

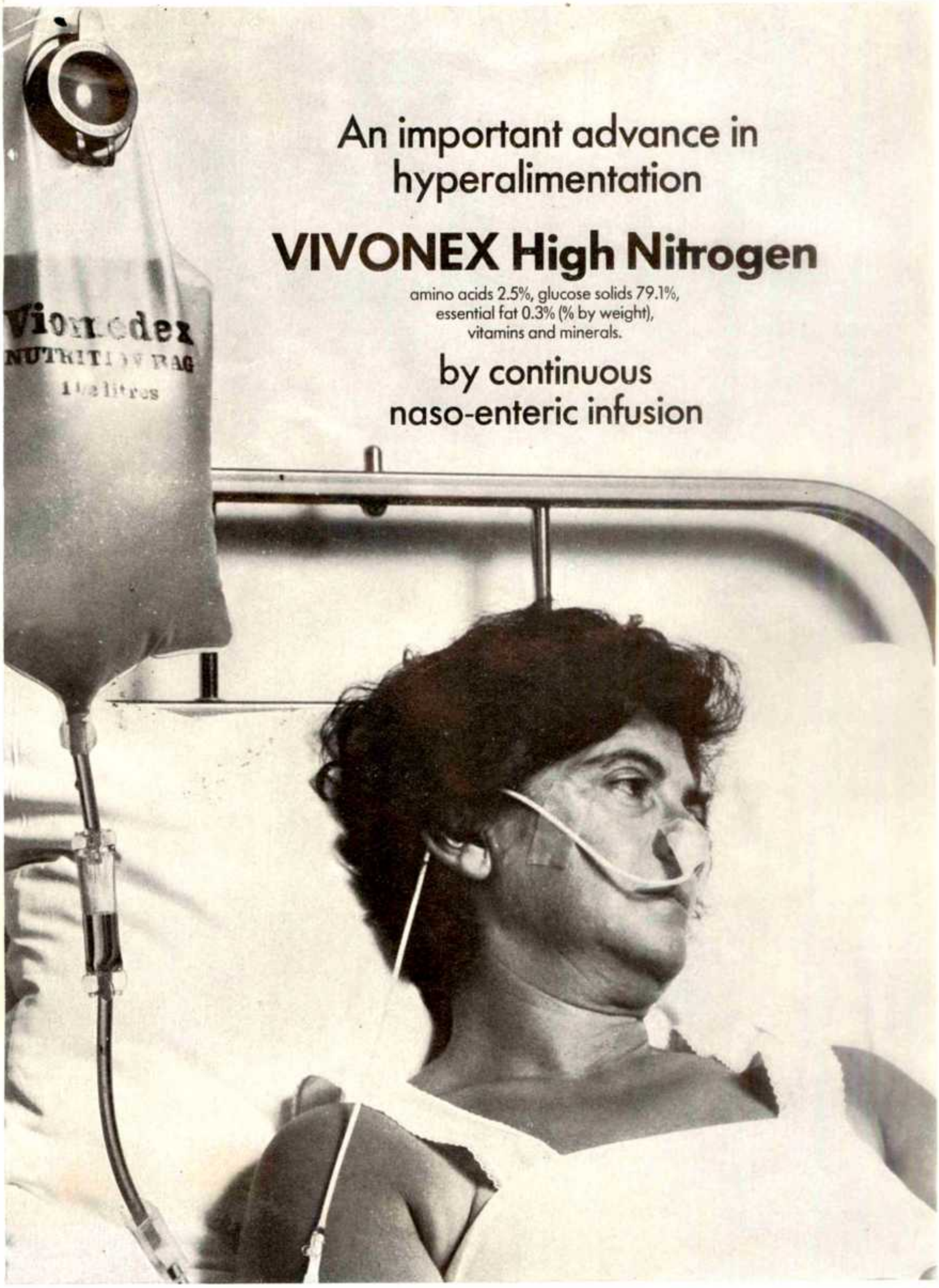
Gastric emptying
The food-barium meal (altogether 350 ml) consisted of two scrambled eggs, salt, 50 ml of milk, one thick slice of bread and 100 ml of Mixobar (Astra). The ingredients were homogenized and the consistency of the meal was semi-solid (4·25 Mattson units). The emptying time was determined from hourly abdominal radiographs. The patients were upright or sitting between the examinations. The test was finished when complete emptying of the gastric contrast medium was observed. The examinations were made preoperatively and at 2 and 12 months after HSV.

Statistical methods
A Hewlett–Packard 9810 A calculator was used for calculating means and s.e. means and an unpaired *t* test program and two-tailed table for estimating probabilities.

Results

The effect of HSV on gastric acid secretion in both groups is shown in *Figs.* 1 and 2. The BAO was similar in both groups before and after vagotomy. In group 1 BAO at 2 months was 0·55 ± 0·17 (mean reduction 86·9 per cent). The corresponding values in group 2 were 0·56 ± 0·21 (mean reduction 87·8 per cent). One year after operation there was an increase in BAO in group 1 to 1·30 ± 0·32 (mean reduction 69·0 per cent) and in group 2 to 1·61 ± 0·49 (mean reduction 65·0 per cent). There were no statistically significant differences between the groups.

PAO$_{pg}$ was also very similar in both groups after HSV. At two months PAO$_{pg}$ was 11·31 ± 1·62 (mean reduction 71·3 per cent) in group 1 and 9·63 ± 1·76 (mean reduction 75·4 per cent) in group 2. There was a slight subsequent increase in the pentagastrin response during the first year to 18·71 ± 2·22 (mean reduction 52·5 per cent) in group 1 and to 14·49 ± 2·19 (mean reduction 62·9 per cent) in group 2. No statistical differences were observed between the groups.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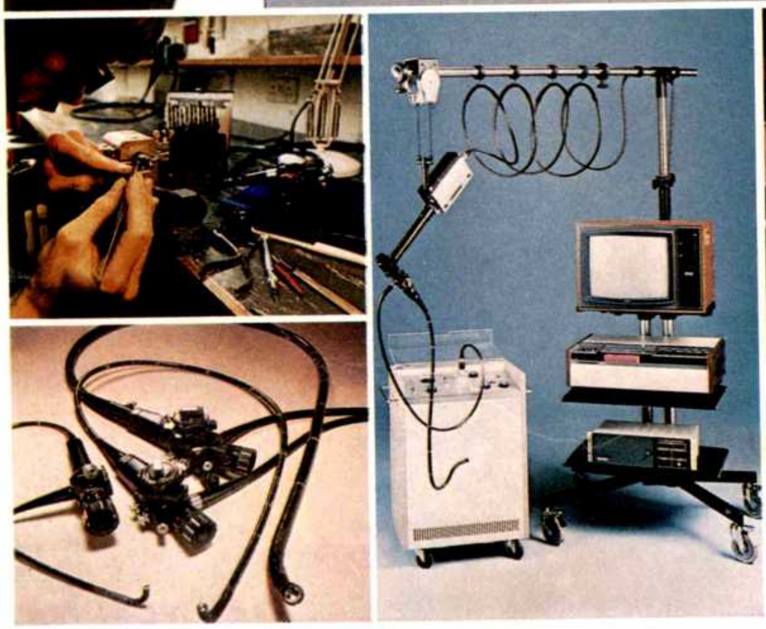

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As regards the postoperative insulin-stimulated gastric acid secretion, the peak acid outputs were again surprisingly similar in both groups. In both groups a definite increase of $\mathrm{PAO_I}$ occurred between 2 and 12 months after HSV (*Table II*). The results of postoperative insulin tests, according to the criteria of Ross and Kay (1964) are shown in *Table III*. There were no early positive responses either at 2 months or at 1 year after HSV in the groups. However, late positivity was twice as common in group 2 as in group 1. This difference was not present in the early postoperative determinations, but became evident 1 year after surgery.

A comparison between postoperative basal serum gastrin values in the groups showed one definite difference between the groups (*Table IV*). After HSV the values increased significantly in both groups ($P<0{\cdot}05$ in group 1, $P<0{\cdot}005$ in group 2), but the mean gastrin value 1 year after operation was significantly higher ($P<0{\cdot}005$) in group 2 than in group 1.

Postoperatively, none of the patients in either group showed clinical signs of gastric retention. Measurements of gastric emptying time showed no significant differences between pre- and postoperative values. The mean preoperative emptying time was 3·3 h, as compared with 3·4 h 2 months and 3·5 h 12 months respectively after HSV.

Table II: INSULIN-STIMULATED SECRETION 2 MONTHS AND 1 YEAR AFTER HIGHLY SELECTIVE VAGOTOMY

Group	$\mathrm{PAO_I}$ (mmol/h; mean±s.e. mean) 2 mth postop.	1 yr postop.
1	1·5±0·4	4·4±1·1
2	1·3±0·5	4·5±1·2

Table III: INSULIN POSITIVE RESPONSES 2 MONTHS AND 1 YEAR AFTER HIGHLY SELECTIVE VAGOTOMY

	2 mth postop.		1 yr postop.	
Group	Early +ve	Late +ve	Early +ve	Late +ve
1	0/35	4/35	0/35	11/35
2	0/35	5/35	0/35	22/35

* Criteria of Ross and Kay (1964).

Table IV: EFFECT OF HIGHLY SELECTIVE VAGOTOMY ON BASAL SERUM GASTRIN CONCENTRATIONS

Group	Preoperative basal gastrin (pmol/l; mean±s.e. mean)	Basal gastrin 1 yr postop. (pmol/l; mean±s.e. mean)
1	36·5±3·1	42·5±6 0
2	36·4±4·0	81·7±7·4

Discussion

Most surgeons use the distribution of branches of the nerves of Latarjet to define the corpus–antrum boundary when they perform HSV. It has been shown, however, for instance by Poppen et al. (1976) who took mucosal biopsies through a gastrotomy, that this landmark corresponds to the corpus–antrum border in only 47 per cent of patients. In the present study we observed that in 22 of the 35 cases the branching of the nerves of Latarjet did not define the boundary between acid-secreting and antral mucosa. The difference could be due to the fact that the distance between mucosal biopsies in Poppen's study was 2 cm while our method allowed continuous monitoring of the mucosa. In any case, it appears to be certain that the distribution of the branches of the nerve of Latarjet does not always define the boundary between acid-secreting and antrum-type mucosa. This means that, in a certain percentage of patients, innervated parietal-cell-containing mucosa remains in the stomach when the HSV is performed using these landmarks. Does this have any clinical significance?

Our results show that there were no differences in the postoperative gastric acid secretions of the two groups when anatomical landmarks were used or the boundary was defined exactly using intraoperative measurements. Unfortunately, this study was not a properly randomized investigation but the preoperative data showed that the groups were well matched. Also, we tried to standardize our operative technique by ensuring that both groups of surgeons used the same anatomical landmarks in determining the distal end-point of dissection. Measurements on acid secretion were done in a similar way by nurses who had had several years' experience and gastrin determinations were carried out in the same laboratory. Thus, we believe we can conclude that intraoperative mapping is not needed to define the corpus–antrum border in HSV because the reduction in acid secretion postoperatively is similar whether anatomical landmarks or intraoperative measurements are used. Also, our results on the effect of HSV on gastric acid secretion are quite comparable with those reported by others (Johnston, 1975).

Our experience with pH-metry also indicates that complete denervation of acid-secreting cells in at least some patients leads to cutting of nerve branches that anatomically could be considered as 'antral'. This is at variance with the observations of Amdrup and Jensen (1970) who, using intragastric pH-metry, found that the corpus–antrum border was situated quite high—8–9 cm above the pylorus. It is difficult to explain why our experience has been different. During our mapping procedures we could confirm the observations of Grassi (1971) and Larsson (1973) that division of vagal branches to the acid-secreting area renders the mucosa temporarily unresponsive to pentagastrin stimulation.

In both groups a clear rise in basal serum gastrin (the stomach was not aspirated before blood sampling) following highly selective vagotomy was observed. This has been reported by others too (for review *see* Stadil, 1977). The mean postoperative serum gastrin was much lower in the unmapped group than in the group in which mapping was performed. Our upper normal value is 50 pmol/l, so the mean serum gastrin concentration in group 2 is clearly pathological. This could be thought to be due to gastric retention in these patients. There were no clinical signs of retention, however, nor did the X-ray study show any retention.

Malmstroem et al. (1977) have suggested that, in man, the antral vagal branches would have an inhibitory effect on gastrin release, which could explain those authors' observation that truncal vagotomy is followed by increased serum gastrin and increased antral gastrin concentrations. In our group 2 a more extensive antral division of the vagal branches was performed. If these branches have an inhibitory effect on gastrin release, that would result in higher postoperative serum gastrin values. The clinical consequences of hypergastrinaemia (as measured by radioimmunoassay) are not known, but this must be considered as an undesirable result. As the effects of the operation on acid secretion were similar in both groups studied, we conclude that mapping of the corpus–antrum border is not needed in highly selective vagotomy.

Acknowledgement

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References

AMDRUP E. and JENSEN H. E. (1970) Selective vagotomy of the parietal cell mass preserving innervation of the undrained antrum. *Gastroenterology* 59, 522–527.

BARON J. H. (1973) The clinical application of gastric secretion measurements. *Clin. Gastroenterol.* 2, 293–314.

BURGE H. and VANE J. R. (1958) Method of testing for complete nerve section during vagotomy. *Br. Med. J.* 1, 615–618.

GOLIGHER J. C. (1974) A technique for highly selective parietal cell or proximal gastric vagotomy. *Br. J. Surg.* 61, 337–345.

GRASSI G. (1971) A new test for complete nerve section during vagotomy. *Br. J. Surg.* 58, 187–191.

JOHNSTON D. (1975) Highly selective vagotomy. *Prog. Surg.* 14, 1–45.

JOHNSTON D. and WILKINSON A. R. (1970) Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer. *Br. J. Surg.* 57, 289–296.

LARSSON J. O. (1973) Demonstration of a refractory period of the parietal cell after vagotomy with special reference to the Grassi test. *Chir. Gastroenterol.* 7, 367–376.

MALMSTROEM J., STADIL F. and CHRISTENSEN K. C. (1977) Effect of truncal vagotomy on gastroduodenal content of gastrin. *Br. J. Surg.* 64, 34–38.

POPPEN P., DELIN A. and SANDSTEDT B. (1976) Parietal cell vagotomy. *Acta Chir. Scand.* 142, 251–255.

ROSS B. and KAY A. W. (1964) The insulin test after vagotomy. *Gastroenterology* 46, 379–386.

STADIL F. (1977) Gastrin and vagotomy. In: NYHUS L. M. and WASTELL G. (ed.) *Surgery of the Stomach and Duodenum*, 3rd ed. Boston, Mass., Little Brown, pp. 121–124.

YALOW R. S. and BERSON S. A. (1970) Radioimmunoassay of gastrin. *Gastroenterology* 58, 1–14.

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Br. J. Surg. Vol. 66 (1979) 39–42

Results of proximal gastric vagotomy over 1–5 years in a district general hospital

D. A. MAKEY, F. I. TOVEY AND R. J. HEALD*

SUMMARY

One hundred and seventy-three patients underwent proximal gastric vagotomy for duodenal ulceration over a 6-year period. One hundred and fifteen of these have been followed up for 1–5 years. The operative mortality was nil and the result was satisfactory in 91 per cent. The incidence of side effects was small, notably that of dumping being 2·4 per cent and of diarrhoea, 3·6 per cent. Incidence of postoperative heartburn was reduced from 13 per cent to 4 per cent by the introduction of hepatic interposition.

The incidence of recurrent ulceration was 5·1 per cent after an average interval of 2 years and that of new gastric ulceration 2·6 per cent after an average of 4 years. There were no recurrent ulcers in those who had peroperative Burge tests, although secretory studies showed no difference between those tested and those not tested. Most recurrences occurred in the earliest cases operated on before Burge testing was introduced and when only 2 cm of the lower oesophagus were exposed.

SEVERAL centres have reported varying recurrence rates after proximal gastric vagotomy (Johnston and Wilkinson, 1970; Grassi et al., 1973; Amdrup et al., 1974; Kronborg and Madsen, 1975; Amdrup et al., 1977; Holst-Christensen, 1977; Dorricott et al., 1978; Goligher et al., 1978).

Our aim is to present the results of elective proximal gastric vagotomy (PGV) for duodenal ulcer in a district general hospital and to assess its efficiency in this situation.

Patients and methods

One hundred and seventy-three patients with duodenal ulcer have undergone PGV without drainage in Basingstoke District Hospital since April 1971. One hundred and fifteen of these have now been followed up for 1–5 years.

All patients had a duodenal ulcer demonstrated radiologically, endoscopically or both. All had elective or semi-elective operations following bleeding that had stopped.

The patients fell into two groups according to the practice of the operating team concerned (*Table I*).

The majority of patients in group 1 had pre- and post-operative pentagastrin tests (3 months or more after PGV) and peroperative Burge tests, except for the first 15 cases which were operated upon before the Burge test was introduced, these having insulin tests instead (again 3 months post-operatively). All the operations were performed by one surgeon (F. I. T.).

Group 2 cases had no acid studies carried out and no per-operative monitoring. The operations were performed by 5 surgeons of differing experience, although just over half were done by one experienced surgeon (R. J. H.).

The operative technique was basically the same in each group. The dissection was taken from the crow's foot up the lesser curve, 'ring barking' the oesophagus for 4–5 cm, with the exception of the first 15 cases in group 1 in which the dissection was taken about 2 cm on to the oesophagus, as originally described by Amdrup and Jensen (1970). The only minor difference was that group 2 patients routinely had division of the left triangular ligament and interposition of the left lobe of the liver between the freed lesser omentum and the bared lesser curve at the end of the procedure.

Table I: DURATION OF FOLLOW-UP FOR EACH GROUP OF PATIENTS

	Duration of follow-up (yr) 5	4	3	2	1	<1	No record
Group 1	14	13	17	11	18	17	1
Group 2	—	5	15	10	12	35	5
Total	14	18	32	21	30	52	6

Table II: OCCURRENCE OF SYMPTOMS AND VISICK GRADING AT TIME OF FOLLOW-UP

	No. of patients	%	
Symptoms			
Non-ulcer dyspepsia	21	12	
Heartburn	15	9	
Food vomiting	2	1·2	
Bile vomiting	—	—	
Small meals	10	6	
Dumping (early and late)	4	2·4	
Diarrhoea	6	3·6	
Grades			
1 Asymptomatic	115	69	}91
2 Trivial symptoms	37	22	
3 More persistent symptoms but no ulcer	6	3·6	
4 Recurrence (plus gastric ulcers)	9	5·4	

Secretory studies

All nasogastric tubes were radiologically positioned in the stomach opposite the angulus.

Pentagastrin tests: Resting juice was collected over one hour for the basal acid output, followed by the injection of pentagastrin (6 μg/kg) intramuscularly and the collection of gastric juice for a further hour to obtain the maximal acid output. Histamine (4 mg/kg) was used in the first 15 cases instead of pentagastrin.

Insulin tests: Four fasting samples at 15 min intervals were taken and the sample with the highest concentration was taken for the basal acid concentration. The samples were pooled for the basal acid output. Soluble insulin (0·15 U/kg) was given intravenously and aspirates collected at 15-min intervals for 2 h. The insulin test was deemed positive if three or more of the following criteria were positive:

1. A rise of 20 mmol/l over basal concentration in either the first or second hour (Hollander, 1946, 1948).
2. A basal acid output of more than 2 mmol/h (Bachrach, 1962).
3. An increase of more than 2 mmol in output over the basal hour in either of the post-insulin hours (Bank et al., 1967).
4. An increasing volume after insulin (Waddell, 1957).
5. A fall of less than 60 per cent in maximal acid output with either pentagastrin or histamine.

The Burge tests were all conducted according to the method of Burge and Vane (1958). All patients were followed up routinely at 3 months, 6 months and yearly thereafter. Defaulters were sent a questionnaire, which yielded a good response. This resulted in 88 per cent of patients having completely up-to-date records, follow-up being incomplete in 9 per cent and 3 per cent being untraceable since their operation.

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Table III: RELATIONSHIP OF THE FALL IN BAO AND MAO TO THE OPERATIVE RESULTS

	Average age (yr)	Average duration of history (yr)	Acid output (mmol HCl) Preop. BAO	MAO	Postop. BAO	MAO	% fall BAO	MAO
Satisfactory result ($n = 42$)	45	10	5·1	28·5	1·14	11·4	78	60
Recurrence ($n = 4$)	32	9	7·3	30	3	17·5	59	42
Non-ulcer dyspepsia ($n = 8$)	40	8	4·6	28·3	0·96	10·6	79	62
First 15 in group 1 ($n = 11$)	42	13	5·9	31	2·3	13	61	60

Table IV: FALLS IN BAO AND MAO WITH AND WITHOUT THE BURGE PEROPERATIVE VAGAL STIMULATION TEST

	Acid output (mmol HCl) Preop. BAO	MAO	Postop. BAO	MAO	% fall BAO	MAO
Burge test ($n = 28$)	4·9	30	1·05	12·1	78	60
No Burge test ($n = 26$)	5·4	29	1·35	10·9	75	62

Preoperative symptoms were assessed retrospectively for length of ulcer history, periodicity and relief by food. Postoperative side effects were specifically asked for, as was recurrent dyspepsia. Recurrent ulceration was proved by endoscopy and/or laparotomy with the exception of one gastric ulcer that was shown by a barium meal.

Results

The operative mortality was nil. There was no case of lesser curve necrosis. Splenectomy was necessary in 3 patients in whom the spleen was damaged and in 2 patients small oesophageal tears were repaired, otherwise there were no serious operative complications. Postoperative recovery was invariably rapid. Nasogastric tubes were used in most of group 1 patients but not in group 2 and the tubes were generally removed on the second day. Fluids were started early and a light diet was commenced on the third day. No postoperative gastric retention was seen except in one patient who probably had significant pyloric stenosis before operation and on whom no definitive pyloric procedure was undertaken at surgery.

The results were divided into four groups corresponding approximately to Visick grading. The overall incidence of dumping, early or late, was 2·4 per cent (4 cases), which was very mild in all cases and required no treatment. Six patients (3·6 per cent) had episodic diarrhoea, but not severe enough to warrant treatment. Persistent anaemia, weight loss or bile vomiting were not seen. Fifteen patients had heartburn or reflux, of whom 12 were in group 1 and had not had hepatic interposition (*Table II*).

In estimating recurrence rates, only the group with a 1–5-year follow-up has been considered. Thirty patients complained at some stage of recurrent epigastric pain. Six of these (5·1 per cent) were found to have a recurrent duodenal ulcer and 3 (2·6 per cent) a new gastric ulcer. Of the remaining 21, 6 had negative endoscopic examination, 2 negative barium meals and 13 only transient dyspepsia for a few weeks, not severe enough to merit investigation or treatment.

Two of the recurrent duodenal ulcers presented within the first year, 2 at 2 years and 2 at 3 years; all were in male patients. Four of the recurrences were among the first 15 patients in group 1. Further surgery was required in 3 of these (1 revision vagotomy, 1 truncal vagotomy and antrectomy and 1 Polya gastrectomy) and in the other patient the ulcer healed and has not recurred. One patient in group 2 has refused further surgery and one has only mild, infrequent symptoms. None of these patients has developed any complications.

The 3 gastric ulcers occurred at between 3 and 5 years. Two of these ulcers have been shown by endoscopy and 1 by radiology to have healed on medical treatment (2 with cimetidine, 1 with carbenoxolone) and the patients at present have no pain.

There were 54 patients in whom complete pre- and postoperative pentagastrin tests had been performed, including 4 patients with recurrence and 8 from the group of 21 patients already mentioned who had non-ulcer dyspepsia (*Table III*).

The acid fall was less in those with recurrence as a group, although the individual MAO reductions were not predictive in each case (20 per cent, 40 per cent, 56 per cent and 58 per cent). Similarly, those with a satisfactory result as a group had a 60 per cent MAO fall, but there were several individuals with much smaller reductions. The groups with dyspepsia and the first 15 patients in group 1 had results almost identical to those of the satisfactory group.

Eleven of the first 15 patients in group 1 had had insulin tests, which in 5 showed incomplete vagotomy (4 first- and second-hour responses and 1 second-hour response only). Three of these patients developed recurrent ulceration. In addition, the patient with a transient recurrence had an insulin test that was negative at 5 months but became positive (second-hour response but with a low MAO with histamine) at 18 months. The insulin tests, though fewer in number, seem to have equated better with recurrence than the pentagastrin tests, because several of the later cases showed less than 60 per cent reduction in MAO without recurrence.

Burge test

The Burge test was performed in 57 patients. In 5 it was technically unsatisfactory, in 3 no response was obtained and in 2 the response could not be abolished despite repeated further dissections and was thought to be somatic. In 47 cases, therefore, an apparently complete vagotomy was obtained, resulting in no recurrent ulcers, 1 gastric ulcer and 8 cases of non-ulcer dyspepsia. Twenty-eight of these 47 cases also had pentagastrin tests and the results were compared with those in 26 patients who had not had the Burge test. This showed no significant difference in acid fall between these two groups (*Table IV*).

Discussion

To establish its place as the operation of choice for duodenal ulceration PGV must show its superiority over other procedures in terms of operative mortality and lack of side effects—especially dumping—and yet have an acceptably low recurrence rate.

The one cloud on the horizon as far as operative mortality is concerned has been lesser curve necrosis. Varying incidences of this often fatal complication have been reported—1·4 per 1000 in Johnston's (1975) survey. It has been suggested that this can be avoided by careful technique and avoidance of diathermy (Heffernan, 1976), or by reperitonealization of the lesser curve (Halvorsen et al., 1975). Fortunately, there have been no instances of gastric necrosis in our series.

Side effects

The dumping, bile vomiting and late nutritional defects found in some patients after gastrectomy still occur to a lesser extent after truncal vagotomy and drainage. If they are caused by abnormal emptying due to the drainage procedure rather than the vagotomy, then we would expect their incidence to fall almost to nil with PGV. Bilateral selective vagotomy with drainage (de Miguel, 1974) reduced the incidence of diarrhoea from 40 to 20 per cent but did not abolish it completely. Following PGV Johnston reported an incidence of only 2 per cent (Johnston et al., 1972). Our series also shows a low incidence of diarrhoea (3·6 per cent), dumping (2·4 per cent) and bile vomiting (nil).

In addition, the lesser incidence of heartburn in group 2 suggests that heartburn may be reduced by employing hepatic interposition. This procedure was done initially to prevent reinnervation of the lesser curve. An added bonus may be that late reoperation, if required, would be easier.

The overall symptomatic results of PGV have been good, with 91 per cent of patients in Visick grades 1 and 2. The 6 poor results (grade 3) are all due to persistent pain, and 2 of these patients are probably neurotic as no definite ulcer has been found at operation. Two patients probably had an erroneous original diagnosis (by barium meal only). In addition, 4 of the 6 had atypical histories. This emphasizes the importance of eliciting a good history of periodicity and relief by food, and confirmation of the diagnosis by endoscopy as well as by barium meal examination when the history is atypical.

Recurrence

One of the drawbacks of vagotomy that leads to its inferior Visick grading compared with gastrectomy (Goligher et al., 1972) has been the high recurrence rate. It is disputed whether this is due to the intrinsic inability of denervation alone to reduce acid sufficiently to cure an ulcer in all patients, or merely to a high incidence of incomplete vagotomy.

Some authors have tried tailoring their surgery according to the preoperative BAO (Orr, 1962) or to the MAO (Bruce et al., 1959; Small et al., 1967; Robbs et al., 1973), usually adding an antrectomy to the vagotomy when the MAO is above a certain level (25 mmol, Robbs; 50 mmol, Small). In addition, Kronborg (1972, 1974) has persistently demonstrated relationships between risk of recurrence and pre- and postoperative acid secretion.

On the other hand, other authors (Holt and Lythgoe, 1961; Clark et al., 1964) found preoperative acid studies to have no prognostic significance. Tovey et al. (1968) found the biggest falls in MAO after truncal and selective vagotomy in those patients with the highest preoperative acid levels. Johnston et al. (1975) have suggested that PGV alone is sufficient even for hypersecretors (MAO more than 50 mmol/h in men) so long as incomplete vagotomy can be avoided. Burge also believed that almost all recurrences after vagotomy were due to leaving intact vagal fibres, commonly small accessory posterior trunks in the case of truncal vagotomy (Burge et al., 1970). Although good figures for selective vagotomy have been reported (Griffith et al., 1972; Amdrup, 1973; de Miguel, 1974), the fact that no completely standardized technique was developed probably led to many incomplete vagotomies in other hands.

With PGV, however, as long as the dissection is taken sufficiently high on the oesophagus, there appears to be less risk of an incomplete vagotomy; indeed, the danger with some techniques (Burge and Frohn, 1969) may be of damaging the main posterior vagus inadvertently. If a complete vagotomy will cure almost any ulcer, great pains must be taken to achieve this. The incidence of incomplete vagotomy fell during this study—possibly aided by the Burge test—in group 1. In this group, however, the introduction of the Burge test coincided with a more extensive dissection of the lower oesophagus.

The fact that the pentagastrin tests with and without the Burge vagotometer reveal no differences reflects either the fallibility of secretory studies or, perhaps, indicates that complete vagotomy is now being achieved without Burge testing.

It seems appropriate, therefore, especially for surgeons learning the technique of proximal gastric vagotomy, to have some form of quality control, at least early on. The best is probably the Burge test, as the vagotomy, if incomplete, can be completed at the time of operation. One of the present authors (F. I. T.) continues to use the Burge test because about 1 in 3 of the patients has an initial positive response despite an apparently complete dissection. The division of further strands of possible nerve tissue usually produces a negative response. Pre- and postoperative acid studies are also helpful, but less so because the result is not known until 3 months later. Once the technique has been mastered, however, these controls may be unnecessary, as an adequate vagotomy may be intrinsically easier to achieve with proximal gastric vagotomy than with other forms of vagotomy.

References

AMDRUP E. (1973) *Clinics in Gastroenterology*. Philadelphia, Saunders, pp. 397–412.

AMDRUP E., ANDERSEN D. and JENSEN H. E. (1977) Parietal cell (highly selective or proximal gastric) vagotomy for peptic ulcer disease. *World J. Surg.* **1**, 19–27.

AMDRUP E. and JENSEN H. E. (1970) Selective vagotomy of the parietal cell mass preserving innervation of undrained antrum. *Gastroenterology* **59**, 522–527.

AMDRUP E., JENSEN H. E., JOHNSTON D. et al. (1974) Clinical results of parietal cell vagotomy (highly selective vagotomy) two to four years after operation. *Ann. Surg.* **180**, 279–284.

BACHRACH W. H. (1962) Laboratory criteria for the completion of vagotomy. *Am. J. Dig. Dis.* **7**, 1071–1085.

BANK S., MARKS I. N. and LOUW J. H. (1967) Histamine and insulin-stimulated gastric acid secretion after selective and truncal vagotomy. *Gut* **8**, 36–41.

BRUCE J., CARD W. I., MARKS I. N. et al. (1959) The rationale of selective surgery in the treatment of duodenal ulcer. *J. R. Coll. Surg. Edinb.* 4, 85–104.

BURGE H. and FROHN M. J. N. (1969) The technique of bilateral selective vagotomy with the electrical stimulation test. *Br. J. Surg.* 56, 452–460.

BURGE H., STEDEFORD R. D. and HOLLANDERS D. (1970) Recurrent ulcer after vagotomy and drainage with the electrical stimulation test, 1957–1969. *Br. Med. J.* 3, 372–375.

BURGE H. and VANE J. R. (1958) Method of testing for complete nerve section during vagotomy. *Br. Med. J.* 1, 615–618.

CLARK C. G., MURRAY J. G., SLESSOR I. M. et al. (1964) Complete vagotomy and its consequences: follow up of 146 patients. *Br. Med. J.* 2, 900–903.

DORRICOTT N. J., MCNEISH A. R., ALEXANDER-WILLIAMS J. et al. (1978) Prospective randomized multicentre trial of proximal gastric vagotomy or truncal vagotomy and antrectomy for chronic duodenal ulcer: interim results. *Br. J. Surg.* 65, 152–154.

GOLIGHER J. C., HILL G. L., KENNY T. E. et al. (1978) Proximal gastric vagotomy without drainage for duodenal ulcer: results after 5–8 years. *Br. J. Surg.* 65, 145–151.

GOLIGHER J. C., PULVERTAFT C. N., IRVIN T. T. et al. (1972) Five-to-eight-year results of truncal vagotomy and pyloroplasty. *Br. Med. J.* 1, 7–13.

GRASSI G., GRECCHIA G., SHUELZ B. et al. (1973) Early results of the treatment of duodenal ulcer by ultraselective vagotomy without drainage. *Surg. Gynecol. Obstet.* 136, 726–728.

GRIFFITH C. A., LEYSE R. M., DAVID D. R. et al. (1972) Mortality and recurrent ulcer after selective vagotomy and pyloroplasty. *Am. J. Surg.* 38, 504–508.

HALVORSEN J. F., HEIMANN P., SOLHAUG J. H. et al. (1975) Localized avascular necrosis of lesser curve of stomach complicating highly selective vagotomy. *Br. Med. J.* 2, 590–591.

HEFFERNAN S. J. (1976) Lesser curve necrosis after proximal vagotomy. *Br. Med. J.* 1, 398–399.

HOLLANDER F. (1946) Insulin tests for presence of intact nerve fibres after vagal operation for peptic ulcer. *Gastroenterology* 7, 607–614.

HOLLANDER F. (1948) Laboratory procedures in the study of vagotomy with particular reference to the insulin test. *Gastroenterology* 11, 419–425.

HOLST-CHRISTENSEN J., HART HANSEN O., PEDERSEN T. et al. (1977) Recurrent ulcer after proximal gastric vagotomy for duodenal and prepyloric ulcer. *Br. J. Surg.* 64, 42–46.

HOLT R. L. and LYTHGOE J. P. (1961) Ten-year results of vagotomy and gastrojejunostomy in the treatment of chronic duodenal ulcer. *Br. J. Surg.* 49, 255–260.

JOHNSTON D. (1975) Operative mortality and postoperative morbidity of highly selective vagotomy. *Br. J. Surg.* 62, 160.

JOHNSTON D., HUMPHREY C. S., WALKER B. E. et al. (1972) Vagotomy without diarrhoea. *Br. Med. J.* 3, 788–790.

JOHNSTON D., PICKFORD I. R., WALKER B. E. et al. (1975) Highly selective vagotomy for duodenal ulcer: do hypersecretors need antrectomy? *Br. Med. J.* 1, 716–718.

JOHNSTON D. and WILKINSON A. R. (1970 Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer *Br. J. Surg.* 57, 289–296.

KRONBORG O. (1972) Influence of the number of parietal cells on risk of recurrence after truncal vagotomy and drainage for duodenal ulcer. *Scand J. Gastroenterol.* 7, 423–431.

KRONBORG O. (1974) Gastric acid secretion and risk of recurrence of duodenal ulcer within 6–8 years after truncal vagotomy and drainage. *Gut* 15, 714–719.

KRONBORG O. and MADSEN P. (1975) A controlled randomized trial of highly selective vagotomy versus selective vagotomy and pyloroplasty in the treatment of duodenal ulcer. *Gut* 16, 268–271.

DE MIGUEL J. (1974) Late results of bilateral selective vagotomy and pyloroplasty for duodenal ulcer: 5–9 year follow up. *Br. J. Surg.* 61, 264–269.

ORR I. M. (1962) Selective surgery for peptic ulcer: a review. *Gut* 3, 97–105.

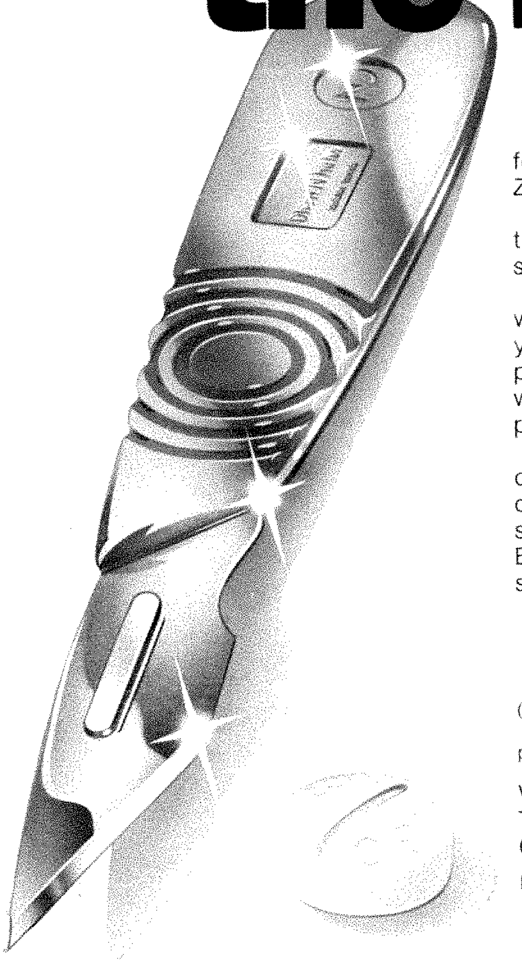
ROBBS J. V., BANK S., MARKS I. N. et al. (1973) Selection of operation for duodenal ulcer based on acid secretory studies: a reappraisal. *Br. J. Surg.* 60, 601–605.

SMALL W. P., BRUCE J., FALCONER C. et al. (1967) The results of a policy of selective surgical treatment of duodenal ulcer. *Br. J. Surg.* 54, 838–841.

TOVEY F. I., SWAMINATHAN M., PARKER K. et al. (1968) Effect of vagotomy on the gastric secretion of acid chloride and pepsin in response to an antral stimulus and to insulin and maximal histamine stimulation. *Gut* 9, 659–666.

WADDELL W. R. (1957) The acid secretory response to histamine and insulin hypoglycemia after various operations on the stomach. *Surgery (St Louis)* 42, 652–658.

Paper accepted 26 June 1978.



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[1] *Ann. intern. Med.* (1977), **87**, 404.
[2] *Brit. med. J.* (1977), **2**, 1302.
[3] *J. Urol.* (1977), **117**, 690.

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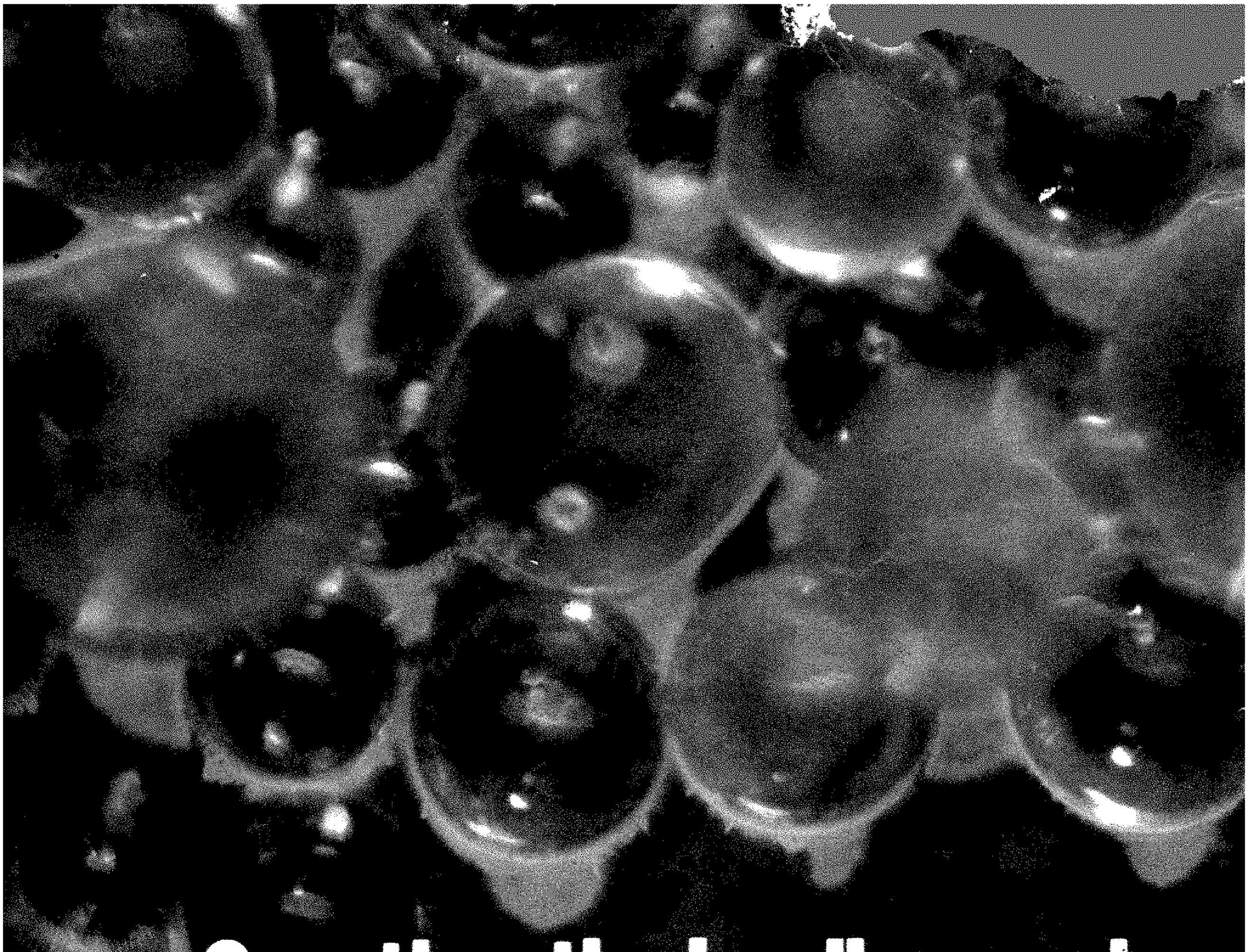

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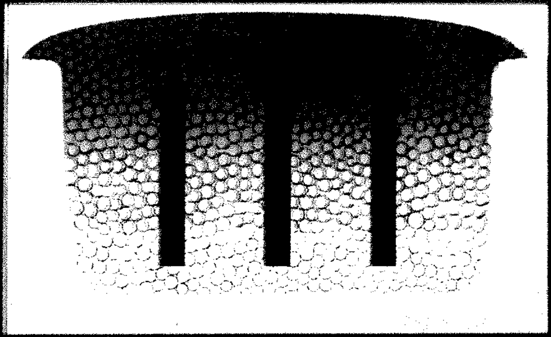

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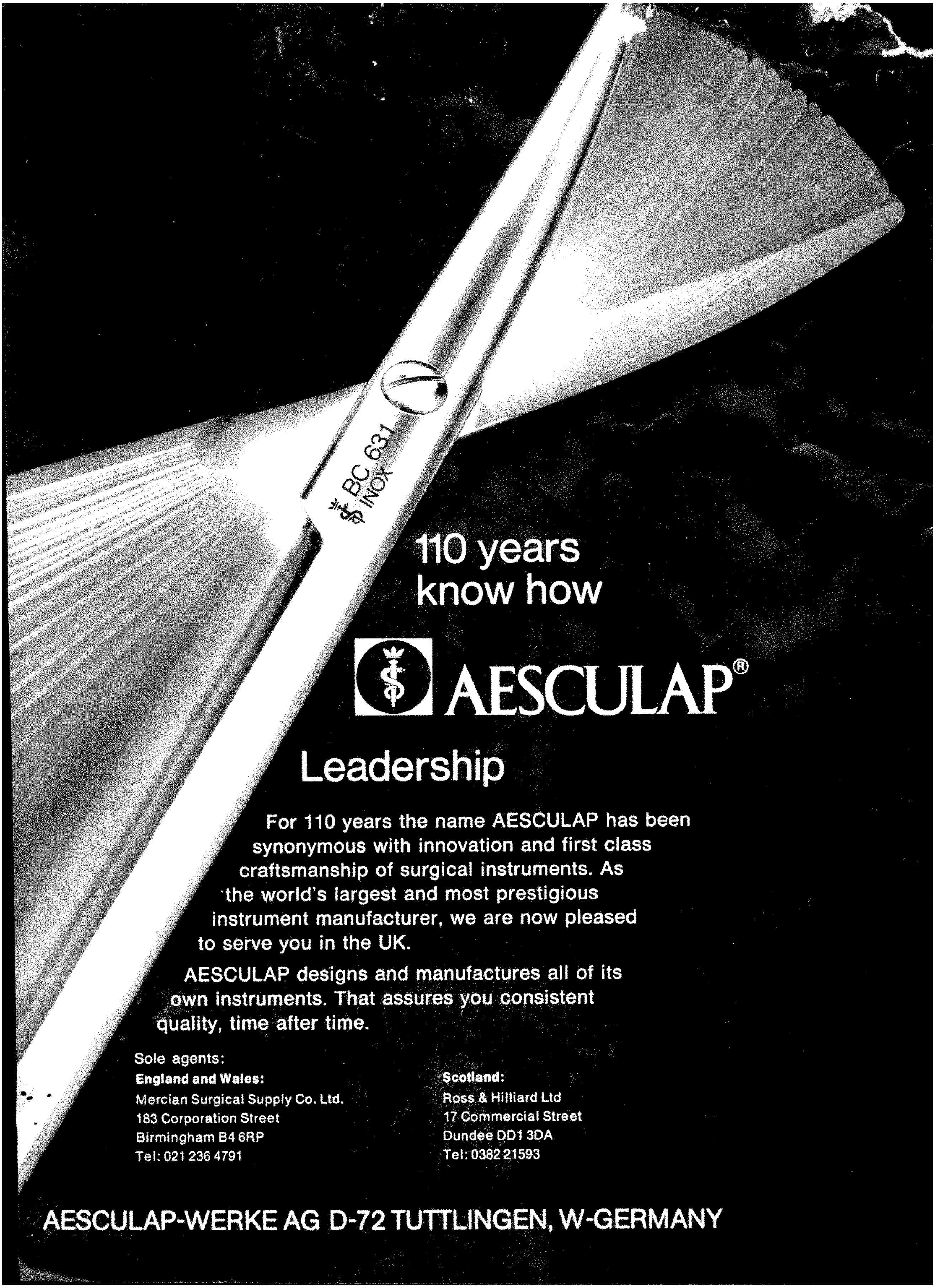

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Highly selective vagotomy with excision of the ulcer compared with gastrectomy for gastric ulcer in a randomized trial

H. L. DUTHIE AND C. J. BRANSOM*

SUMMARY

Fifty-six patients with benign gastric ulcer of the body of the stomach have been entered into a randomized trial of highly selective vagotomy with excision of the ulcer (HSVE) (26 cases) against standard Billroth I partial gastrectomy (BI) (30 cases). The operations were carried out by all grades of surgical staff. No patient died within 1 month of operation. Postoperative morbidity was greater after gastrectomy than after HSVE. At an average follow-up of about 4 years, functional results according to a modified Visick classification were similar in both groups, with about 75 per cent good results. Two recurrent ulcers occurred after gastrectomy (7 per cent) and 4 after HSVE (15 per cent). Neither operation has a distinct advantage at this stage.

SIMPLE gastric ulcer of the body of the stomach is usually treated by partial gastrectomy with gastroduodenal (Billroth I) anastomosis when the patient's symptoms warrant surgery. This operation has been reported to have a recurrence rate of 0–5 per cent in various series (Duthie, 1970). Other postgastrectomy symptoms occur, although fewer than after gastrojejunal (Polya) anastomosis. Many of the postprandial symptoms after gastrectomy are attributed to lack of control of emptying. Attempts have been made to remedy this by forms of 'pylorus-preserving' gastrectomy, which have had excellent results with no recurrent ulcers in 60 patients followed for 1–9 years (Sekine et al., 1975). Other groups have not been able to reproduce these results, with either an unacceptably high recurrence rate at 13 per cent (Jorgensen et al., 1974) or a poor symptomatic result (Buhl and Campbell, 1974). Our approach to retention of some control of gastric emptying has been to leave the innervated antrum *in situ* by performing a highly selective vagotomy (Amdrup and Jensen, 1970; Johnston and Wilkinson, 1970). We already have experience of a controlled comparison of truncal vagotomy and pyloroplasty versus partial gastrectomy for gastric ulcer in 100 patients, and we found no significant symptomatic difference between these two operations after 5 years (Duthie and Kwong, 1973). A similar result was found by Madsen et al. (1976). It was hoped that the avoidance of pyloroplasty in the present study would improve the results of the more conservative procedure. In addition, a full-thickness excision of the ulcer and a surrounding 1 cm of gastric wall has been done to ensure complete histology and also because it may improve the chances of avoiding recurrence (Daniels and Strachan, 1973).

Patients and methods

From July 1971 to July 1977 56 patients entered the trial: all had benign gastric ulceration in the body of the stomach, prepyloric ulcers and combined gastric and duodenal ulcers being excluded. At laparotomy a decision was made as to whether the patients were equally suitable for highly selective vagotomy plus full-thickness excision of the ulcer (HSVE) or Billroth I partial gastrectomy (BI). Six patients were excluded from the trial because they were found to be unsuitable for HSVE, mainly because the ulcer was so placed as to make excision impossible without denervating the antrum.

In HSVE the surgical technique employed was similar to that of Johnston et al. (1972) except that those authors opened the stomach opposite the ulcer to perform an excision biopsy, leaving the ulcer base intact, whereas we excised the ulcer-bearing area from the serosal side. A standard partial gastrectomy with gastroduodenal anastomosis (BI) comprised removal of two-thirds of the stomach.

The 56 patients in the trial were randomized with precautions to ensure equal sex distribution. In those having HSVE the vagal denervation was completed before the excision of the ulcer, which was submitted to immediate histology. No cancer was found at this stage. In the event of malignancy it would have been easy to proceed to gastrectomy, as much of the mobilization would have already been completed. The operations were performed by surgeons in training and by consultant surgeons (30 by consultants; 15 by senior registrars or equivalent; 11 by registrars or equivalent).

An insulin test of gastric acid secretion was performed in 11 patients (42 per cent) 5 days to 27 months after HSVE: this small percentage is due to the fact that many of the women in the series either refused to attempt the test or failed to complete it. After three 15-min collections of basal acid secretions, soluble insulin (0·2 i.u./kg body weight) was injected intravenously and eight further 15-min samples were collected. The tests were performed with the patient semi-recumbent on the left side after a nasogastric tube had been positioned along the greater curvature of the stomach under radiological control. Losses through the pylorus and duodenal reflux were not measured. The response to insulin was calculated as the difference between the basal acid output (BAO) and the peak acid output after insulin (PAO_I) and also expressed as early or late positive using modified Hollander criteria (Johnston et al., 1967).

The patients were interviewed at 3, 6 and 12 months and annually thereafter. The interviewer did not have knowledge of the type of operation performed. Functional results were graded according to a modification of the Visick classification: grade 1, no gastric symptoms; grade 2, mild symptoms easily controlled by slight adjustments to diet or way of life; grade 3, moderate symptoms not controlled by simple manoeuvres and not interfering with social or economic life; grade 4, symptoms as bad as or worse than before operation (patients having recurrent ulceration at any time were assessed as grade 4).

Questions were asked routinely concerning the following symptoms: epigastric fullness, bilious vomiting, food vomiting, early dumping, late dumping, flatulence, heartburn, dysphagia and bowel habit. The severity of these symptoms was estimated in four grades. More reliance can be placed on the *incidence* of symptoms than on their grading (DeDombal et al., 1974).

Results

No patient died within 1 month of operation. HSVE was performed in 26 patients and gastrectomy in 30 patients. The groups were comparable in age (HSVE 53·6 yr, BI mean 56·2 yr) and sex distribution. Six patients have died in the follow-up period, 3 in each operative group. None of the deaths was related to peptic ulcer disease; 3 died of myocardial infarction, 1 of a cerebrovascular accident, 1 of cancer of the pancreas and 1 of bronchopneumonia. These six are included in the morbidity figures but not in the follow-up results, except the one who had a recurrent ulcer. Postoperative morbidity was statistically significantly greater after gastrectomy (*Table I*) but only at the 5 per cent level. Comparison of percentage functional results according to the modified Visick classification at a mean follow-up of about 3 years and about 4 years shows no statistically significant differences (*Table II*), but there are more excellent (grade 1) results and also more grade 4 results after HSVE. If the top two and the bottom two groups of the Visick classification are combined, the results are very similar (*Table II*), with good results in 74–78 per cent of cases. The unsatisfactory results are detailed in *Table III*. Recurrent ulceration has been found in 4 patients after HSVE (15 per cent) and in 2 patients after gastrectomy (7 per cent), 1 having died (*Table IV*) of bronchopneumonia. A partial gastrectomy has been performed in 3 patients after HSVE and in 1 from the gastrectomy group a higher gastrectomy was done with a vagotomy. The results in the small percentage of patients who underwent insulin testing do not permit any conclusions about the value of the response in assessing the risks of recurrence (*Table V*). Most symptoms recorded after operation were more frequent after BI gastrectomy than after HSVE. This difference was only probably statistically significant for postprandial nausea (*Table VI*). It must be remembered that most of these symptoms were mild, and nausea contributed to only 1 patient being placed in Visick grade 3.

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Table I: POSTOPERATIVE MORBIDITY

	Billroth I gastrectomy	Highly selective vagotomy
Chest infection	5	3
Wound infection	5	2
Pulmonary embolus	1	2
Anastomotic leak	2	0
Postoperative bleeding	1	0
Urinary retention	2	0
Gastric retention	4	1
	20*	8*

* Significantly different: $\chi^2 = 4\cdot1$, $P<0\cdot05$.

Table II: VISICK CLASSIFICATION PERCENTAGE

Visick grade	Years of follow-up	Grade 1	2	3	4
Billroth I gastrectomy	3	48	28	20	4
	4	48	26	15	11
Highly selective vagotomy	3	68	20	8	4
	4	61	17	0	22
		Good		Unsatisfactory	
Billroth I gastrectomy	3	76		24	
	4	74		26	
Highly selective vagotomy	3	88		12	
	4	78		22	

Table III: RESULTS IN VISICK GRADES 3 AND 4

Billroth I gastrectomy		
Visick grade 3	Dumping	2
	Diarrhoea and dumping	1
	Epigastric fullness and nausea	1
Visick grade 4	Recurrent ulcer	2
	Dumping and diarrhoea	2
Highly selective vagotomy		
Visick grade 4	Recurrent ulcer	4
	Heartburn, epigastric fullness and dysphagia	1

Discussion

At this early stage in the assessment of the procedures no clear lead can be given as to the eventual outcome. The symptomatic results, with about three-quarters having a good result, are similar to those in other reports (Semb, 1978) and indicate the practicability of using either operation for the surgical management of gastric ulcer. The larger number of patients with no symptoms after HSVE at 3 years did not reach statistical significance and was in contradiction to the early results in our previous comparison of truncal vagotomy and pyloroplasty with Billroth I partial gastrectomy when the gastrectomy patients had superior results 3 years postoperatively, although this advantage was lost by the 5-year follow-up (Duthie and Kwong, 1973). It is interesting that HSVE had lost its potential advantage by the 4-year follow-up stage in the present study.

The technique of highly selective vagotomy is well established in this unit, with over 200 operations having been performed by all grades of staff. Thus the cases reported here have not been treated solely by consultants but also by surgeons in training. If a procedure is to be acceptable on a broad basis it must be tested on a similar scale. The mobilization of the lesser curvature of the stomach in HSVE renders the excision of the ulcer straightforward, except in those cases where it is to be found at the incisura, when the full operation with ulcer excision becomes impossible.

Table IV: RECURRENT GASTRIC ULCERATION

Operation	Sex	Age (yr)	Time of recurrence (mth)	Insulin test	Management
Billroth I gastrectomy	M	68	3		Ulcer unsuspected and found at autopsy. Died of bronchopneumonia 3 mth postop.
	M	52	12		Vagotomy and Polya gastrectomy at 3 yr
Highly selective vagotomy	F	40	7	Early +ve	Billroth I gastrectomy at 3 yr
	F	44	15	Not done	Healed on carbonoxolone
	F	69	8 suspicious 36 proved	−ve	Billroth I gastrectomy at 4 yr
	M	54	6 suspicious 36 proved	−ve	Billroth I gastrectomy at 4 yr

Ta[illegible]NSULIN TESTS

			Acid output (mmol/h)		
Patient	Time after operation	Hollander response	BAO	PAO_I	Response to insulin
G. G.	5 d	Early +ve	0	0·5	0·5
V. P.	16 mth	−ve	1·6	0·7	−0·9*
P. M.	5 d	−ve	9·7†	0·7	−9·0
G. M.	5 d	−ve	0	0	0
J. W.	18 mth	Late +ve	11·0†	5·0	−6·0
E. G.	21 d	−ve	0	0	0
J. G.	8 d	−ve	0	1·4	1·4
C. C.	5 d	−ve	12·6†	4·5	−8·1*
E. C.	5 d	−ve	0·8	1·3	0·5
C. H.	5 d	Early +ve	2·3	4·3	2·0
J. S.	5 d	Early +ve	‡	‡	‡*

* Time of diagnosis of recurrent ulcer: V. P. and C. C., 36 mth; J. S., 7 mth.

† Probably indicates a degree of gastric retention.

‡ Not calculated.

Table VI: POSTOPERATIVE SYMPTOMS: PERCENTAGE INCIDENCE

	Billroth I gastrectomy	Highly selective vagotomy
Ulcer pain*	15	5
Nausea	31**	0†
Bile vomiting	19	5
Food vomiting	15	0
Epigastric fullness	62	40
Early dumping	27	5
Late dumping	12	0
Heartburn	40	35
Flatulence	54	40
Dysphagia	0	10
Episodic diarrhoea	35	15

* Excludes those with proved recurrent ulcer.

† Difference statistically significant ($P<0·05$).

Although ulcer recurrence is largely prevented after HSVE, it can only be as a result of the reduction in the production of acid/pepsin by the stomach since nothing specific has been done to change the amount of biliary reflux, which is thought to play an important part in the aetiology of gastric ulcer (Rhodes and Calcraft, 1973).

The higher percentage (15 per cent) of recurrent ulceration after HSVE is disappointing, although it does not reach statistical significance over gastrectomy (7 per cent). It is higher than the recurrence rate in our series comparing truncal vagotomy and pyloroplasty with gastrectomy (Duthie and Kwong, 1973) but, if one may be permitted to compare different series, not significantly higher. By analogy with recurrent duodenal ulceration after vagotomy, one of the recurrent ulcers could be attributed to incomplete denervation, as shown by the early positive insulin test, but we have not enough information to give any prognostic significance to gastric responses to insulin hypoglycaemia in this series. The number of recurrences may increase, as several patients have had symptoms which they liken to ulcer pain, although endoscopy has shown normal appearances. We already have the experience of two subjects having mild intermittent symptoms for 3 years before a firm diagnosis of recurrent ulcer was established.

By insisting on the excision of the ulcer-bearing area we have abandoned one of the advantages of conservative surgery in the case of the ulcer situated high on the lesser curve, but in return, we have gained the security of a histological study of the full ulcer area.

Thus, from a technical as well as a functional point of view there seems to be no pressing indication to change to highly selective vagotomy with excision in place of Billroth I partial gastrectomy for the surgical treatment of benign gastric ulcer of the body of the stomach.

References

AMDRUP E. and JENSEN H. (1970) Selective vagotomy of the parietal cell mass preserving innervation of the undrained antrum. *Gastroenterology* **59**, 522–527.

BUHL O. and CAMPBELL U. D. (1974) Gastric ulcer treated with segmental resection without pyloroplasty. *Acta Chir. Scand.* **140**, 528–530.

DANIELS H. A. and STRACHAN A. W. B. (1973) Gastric ulcer treated by vagotomy, pyloroplasty and ulcerectomy. *Br. J. Surg.* **60**, 389–391.

DEDOMBAL F. T., HORROCKS J. C. and CLAMP S. E. (1974) Observer variation in the assessment of results of surgery for peptic ulceration. *Gut* **15**, 824 (Abstr.).

DUTHIE H. L. (1970) Vagotomy for gastric ulcer. *Gut* **11**, 540–545.

DUTHIE H. L. and KWONG N. K. (1973) Vagotomy or gastrectomy for gastric ulcer. *Br. Med. J.* **4**, 79–81.

JOHNSTON D., HUMPHREY C. S., SMITH R. B. et al. (1972) Treatment of gastric ulcer by highly selective vagotomy without a drainage procedure: an interim report. *Br. J. Surg.* **59**, 787–792.

JOHNSTON D. and WILKINSON A. R. (1970) Highly selective vagotomy with a drainage procedure in the treatment of duodenal ulcer. *Br. J. Surg.* **57**, 289–296.

JORGENSEN S. J., HALSE C. and POULSON P. E. (1974) Segmental gastric resection for gastric ulcer. *Acta Chir. Scand.* **140**, 635–636.

MADSEN P., KRONBORG O., HANSEN O. H. et al. (1976) Billroth I gastric resection versus truncal vagotomy and pyloroplasty in the treatment of gastric ulcer. *Acta Chir. Scand.* **142**, 151–153.

RHODES J. and CALCRAFT B. (1973) Aetiology of gastric ulcer with special reference to the roles of reflux and mucosal damage. *Clin. Gastroenterol.* **2**, 227–243.

SEKINE T., SATO T., MAKI T. et al. (1975) Pylorus-preserving gastrectomy for gastric ulcer: one to nine year follow-up study. *Surgery* **77**, 92–99.

SEMB L. S. (1978) Billroth I gastrectomy. In: NYHUS L. N. and WASTELL C. (ed.) *Surgery of the Stomach and Duodenum.* Boston, Mass., Little, Brown.

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Long term follow-up of patients with gastric ulcers treated by vagotomy, pyloroplasty and ulcerectomy

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SUMMARY

Vagotomy and pyloroplasty with excision of the ulcer has been performed in a series of 90 patients with benign gastric ulcers. Long term follow-up has shown only 2 patients with recurrent ulceration. Fifty-eight patients with more than 2 years' follow-up attended for personal interview, of whom 96 per cent had a satisfactory result.

In the surgery of benign gastric ulcers, vagotomy and pyloroplasty alone has been associated with a recurrence rate of 5–36 per cent, and in most centres partial gastrectomy has held pride of place in the treatment of gastric ulcers. There is, however, a tendency for gastric ulcers to inhabit a particular site in any one stomach, and if excision of the ulcer is performed at the same time as a vagotomy and drainage procedure, then recurrence rates decrease.

Patients and methods

In the present series, 62 patients were reviewed in 1971 (Daniels and Strachan, 1973). These patients plus a further 28 make up the series of 90 patients. There has been one instance of recurrent gastric ulcer and one of recurrent duodenal ulcer.

Technique

Truncal vagotomy has been the operation of choice. The only patient to have a selective vagotomy later developed a recurrent gastric ulcer. Lesser curve ulcers are excised by opening the stomach close to the ulcer and excising the ulcer from the mucosal surface. The resulting defect is sutured in two layers with chromic catgut. If there is much surrounding thickening it is not always possible to invert the seromuscular layer. A posterior ulcer cannot always be approached via the lesser sac, in which case the ulcer is excised through an anterior gastrotomy.

Results

Ninety patients (57 males, 33 females) in Barrow in Furness have had this operation as the primary procedure between 1963 and 1975. The average age of the patients was 55·5 years (*Table I*).

Thirteen patients presented with bleeding and 5 patients presented with a perforation, all requiring urgent surgery. Twenty-one patients had an associated duodenal ulcer or evidence of there having been one in the past. Four patients had prepyloric ulcers.

Table I: DETAILS OF THE PATIENT SERIES

Died postoperatively	4	
Died subsequently (unrelated causes)	13	
Visick grade 1 (seen) (2 yr follow-up)	3	
Visick grade 1 (seen)	51	96% of long term follow-up patients attending personal interview
Visick grade 2 (seen)	5	
Visick grade 3 (seen)	2	
GP follow-up	4	
Untraceable	6	
Recurrence	2*	
Total	90	

* One gastric and one duodenal ulcer.

Four patients died postoperatively: 2 from pulmonary emboli, 1 from a coronary thrombosis and 1 from bronchopneumonia complicating a possible staphylococcal enteritis (Daniels and Strachan, 1973).

Thirteen patients have died subsequent to the operation—all of unrelated causes: 3 of this group were followed up for less than 2 years and all were Visick grade 1 when last seen. The average follow-up period of the remaining 10 patients was 5 years, when 8 were classified as Visick grade 1 and 1 was Visick grade 2. The tenth patient died 4 years after his operation from a carcinoma of the stomach. The original histology was confirmed as benign.

Six patients were untraceable: 5 had been followed up for 1–4 years and 4 had been classified as Visick 1 grade 1 and 1 as Visick grade 2. The sixth was an Indian seaman who had no follow-up.

Four patients were unable to attend for review, but their general practitioners were contacted and none of these patients appeared to have any gastric symptoms.

Sixty-one patients attended a specially arranged out-patient review and were assessed by the present authors, neither of whom had been involved in the treatment of the patients (the notes were available, however). A modified Visick grading was used (Visick grade 1, symptom-free; Visick grade 2, mild symptoms and no disability; Visick grade 3, moderate symptoms involving some interference with social or economic life; Visick grade 4, recurrent ulcer or severe symptoms or the need for further surgery).

Three patients had a follow-up of less than 2 years—all in Visick grade 1,—whilst the mean follow-up on the remaining 58 patients was 7·5 years. Of these patients, 51 were Visick grade 1, 5 were Visick grade 2 and 2 were Visick grade 3. Of these 2 patients, one had occasional bouts of diarrhoea and the other patient had some indigestion which was well controlled with 'slippery elm'. The latter patient had had further barium studies which had not shown any recurrent ulceration. Both patients stated that there was an improvement on their preoperative condition.

Two patients had recurrent peptic ulceration. One lady aged 73 had had a selective vagotomy (the only one of the series) and suffered a recurrent ulcer 3 years later, adjacent to the old scar. An insulin test meal had shown incomplete vagotomy. She underwent a partial gastrectomy from which she made a good recovery.

A man aged 49 had had a duodenal ulcer as well as a lesser curve ulcer at the original operation. Six months later he had recurrent symptoms and an insulin test meal showed complete vagotomy. At reoperation an active duodenal ulcer was found. A

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[illegible]ectomy was performed and he made a good recovery.

Two patients outside the series had had vagotomy, pyloroplasty and ulcerectomy, and subsequent histology showed carcinoma. One patient had had a partial gastrectomy and the specimen showed no residual tumour; he was well 2 years later. The other patient had had no further procedure and died 18 months later.

Discussion

It has been argued that vagotomy and drainage has a place in the treatment of those patients with both gastric and active (or evidence of previous) duodenal ulceration (Douglas and Duthie, 1971; Kennedy et al., 1972). Clarke et al. (1972), however, had a 10 per cent recurrence rate in this group, and they considered vagotomy and pyloroplasty a satisfactory form of treatment for high and bleeding ulcers. De Miguel (1975) has found no difference in the recurrence rates of either group, and in his long term follow-up of 71 patients undergoing selective vagotomy and pyloroplasty for benign uncomplicated gastric ulcers there was a recurrent gastric ulcer rate of 19 per cent. Postoperative X-ray studies were performed which showed that the ulcer crater healed, in most cases, in 2–3 weeks. In each of the 13 patients with recurrent ulceration the ulcer had formed at the same site as the original lesion. This is, therefore, the rationale of excising the ulcer when the vagotomy and pyloroplasty is performed.

Our results show that of 58 patients attending for long term personal follow-up, 56 have a satisfactory result (Visick grades 1 or 2) and only 2 patients out of the whole series of 90 suffered recurrent ulceration. It has not been routine to perform a postoperative arium meal unless symptoms were in any way suggestive of further ulceration. Endoscopy was not available for the majority of patients. The addition of ulcerectomy to the vagotomy and pyloroplasty procedure might well account for this low recurrence rate.

Local excision of the ulcer is a lesser procedure than partial gastrectomy, producing very little reduction in residual gastric volume; this is particularly true in the case of high gastric ulcers. In addition, in the latter situation a partial gastrectomy may be technically difficult and local excision of the ulcer may be more safely achieved.

On the basis of our figures we would suggest that vagotomy and pyloroplasty with local excision of the ulcer is a procedure worthy of wider adoption in the treatment of gastric ulceration.

Acknowledgements

We wish to thank Mr H. A. Dañiels, Mr A. W. B. Strachan and Mr J. H. Kilshaw for permission to study their patients and also Mrs J. Cornthwaite for her help in tracing the patients.

References

CLARKE R. J., LINCOLN LEWIS D. and ALEXANDER-WILLIAMS J. (1972) Vagotomy and pyloroplasty for gastric ulcer. *Br. Med. J.* **2**, 369–371.

DANIELS H. A. and STRACHAN A. W. B. (1973) Gastric ulcer treated by vagotomy, pyloroplasty and ulcerectomy. *Br. J. Surg.* **60**, 389–391.

DOUGLAS M. C. and DUTHIE H. L. (1971) Vagotomy for gastric ulcer combined with duodenal ulcer. *Br. J. Surg.* **58**, 721–724.

KENNEDY T., KELLY J. M. and GEORGE J. D. (1972) Vagotomy for gastric ulcer. *Br. Med. J.* **2**, 371–373.

DE MIGUEL J. (1975) Recurrence of gastric ulcer after selective vagotomy and pyloroplasty for chronic uncomplicated gastric ulcer: a 5–10-year follow-up. *Br. J. Surg.* **62**, 875–878.

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Pylorectomy and prepyloric antrectomy for gastric ulcer

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SUMMARY

From July 1970 to May 1977 79 patients with chronic gastric ulcer were submitted to a pylorectomy and prepyloric antrectomy (only 4–5 cm of the distal stomach being removed). In most, the excision extended in the form of a narrow tongue along the lesser curvature to include the ulcer. Vagotomy was added when signs of a healed or active duodenal ulcer were seen (19 cases). Associated lesions in the distal stomach were detected in 38 more patients.

Up to the present no recurrence has been observed and functional results have been satisfactory in 90 per cent of patients.

Preliminary results show that this operation produces a satisfactory cure for gastric ulcer, thus making more extensive resections unnecessary.

In the treatment of gastric ulcer there are two types of operative procedure in use today: excisional surgery, mainly represented by a partial gastrectomy, and conservative surgery, represented by vagotomy—truncal, selective or proximal gastric—with or without associated drainage. Of these two approaches, gastric resection has been and still is the operation most widely used.

In recent years, as a result of the writings of Dragstedt (1953), there has been repeated speculation concerning the possible influence of a hyperfunction of the gastric antrum in the formation of a gastric ulcer. Burge (1964) has emphasized the coexistence of associated pyloric lesions (pyloric hypertrophy, mucosal stenosis etc.) which, under the common denomination of 'pyloric channel disease', would contribute in a varied degree towards gastric retention. This in turn, it was suggested, would lead to an antral hyperactivity and the appearance of a gastric ulcer.

At the end of the 1960s, stimulated to some degree by personal observations of the frequent presence of distal gastric-associated lesions (de Miguel, 1970), the present author decided to test resections limited to the last few centimetres of the stomach.

Patients and methods

From July 1970 to May 1977 79 patients (68 males and 11 females) with chronic uncomplicated gastric ulcer were operated on by the author, with excision of the pylorus, about 4–5 cm of the distal stomach and the ulcer. In this operation it was accepted that some part of the antrum would be left with the gastric remnant. The ulcer crater was localized in the antrum in 21 patients, in the incisura angularis in 44 and in the lesser curve in 14. Three patients had two or more ulcers. As the ulcer was included in the resection, it meant, for most of the cases, excision of a variable extent of the lesser curvature (*Figs.* 1, 2).

In 19 cases the antropyloric excision was accompanied by a vagotomy because there were clear radiological and operative signs of past duodenal ulceration. However, the duodenal ulcer only showed itself to be active in one of these cases. The series is not consecutive because other methods were employed for the treatment of gastric ulcer over the same period. Lesions in the juxtacardial position were operated on by vagotomy and drainage for reasons of obvious difficulty and risks.

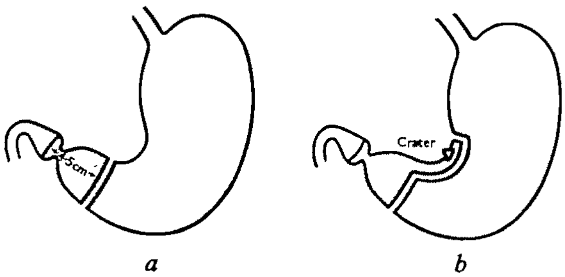

Fig. 1. Diagrammatic representation of prepyloric antrectomy (*a*) and extended to the lesser curve to include the ulcer (*b*).

Apart from the 19 duodenal ulcers mentioned above, pathological manifestations at the distal stomach were observed in another 38 patients (*Table I*). Pyloric hypertrophy was particularly common.

These different associated lesions did not always manifest themselves as duodenopyloric obstruction, although some degree of pyloric stenosis was observed in a few patients.

Follow-up studies

Twenty-five patients had their operation more than 5 years ago; in the other 45, the period of observation varied between 1 and 5 years, with an average of 2–3.

In addition to routine regular reviews, a special examination of almost all patients was carried out during the weeks before the preparation of this paper. A few patients were reviewed by postal questionnaire only. Those who complained of digestive symptoms were examined by X-rays and, when it appeared necessary, by endoscopy. One patient was lost to follow-up.

The 8 deaths during the follow-up period were due to cardiovascular diseases in 4, pneumonia in 1, accidental death in 2 and cancer of the larynx in 1.

Results

Symptoms occurring 1–8 years after the operation are summarized in *Table II*. Bile or food vomiting occurred in 3 patients, all of whom were habitual consumers of large quantities of alcohol. Fullness after meals, found in 16 patients (22 per cent), was usually slight and, in a number of cases, only presented after heavy meals. In 2 patients with associated gastric discomfort, however, fullness was constant and independent of the quantity of food consumed; X-ray and endoscopic examinations revealed the presence of large residues. Both patients were in the group having excision plus vagotomy and in both there was no pyloric obstruction. Symptoms due to milk intolerance were noticed in 23 patients (33 per cent). Early dumping, occurring approximately 30 min after meals, was seen in 12 (17 per cent) and was always mild. Four patients (6 per cent) had epigastric burning; the complaint was mild in 3 but in 1 it was the initial symptom of peptic oesophagitis which led to oesophageal stenosis necessitating surgical intervention.

Seventeen patients had increased in weight by 8–26 kg, with an average of 14 kg. Only 3 showed a

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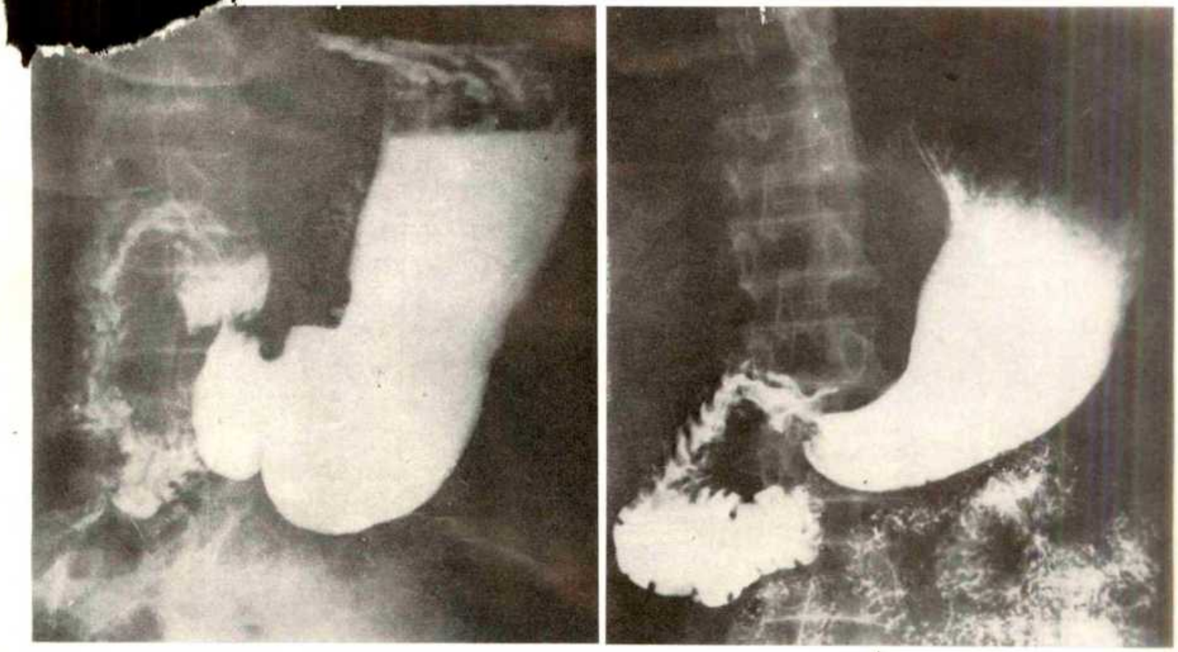
a *b*

Fig. 2. *a*, Barium meal outline of the stomach showing a lesser curve ulcer. *b*, The same patient after prepyloric autrectomy. Note the amount of stomach preserved.

Table I: ASSOCIATED LESIONS (RADIOLOGICAL AND OPERATIVE FINDINGS) IN 79 PATIENTS

Associated lesion	No. of patients
Hypertrophy of pyloric musculature	26
Antral distortion (atresia of antrum)	6
Mucosal pyloric rigidity	6
Duodenal ulcer	19
No associated lesion	20
Not recorded	2

Table II: SYMPTOMS 1–8 YEARS AFTER OPERATION

Symptoms	No. of patients		%
Food vomiting	2		2·9
Bile vomiting	1		1·4
Fullness after meals	16		22·8
Milk intolerance	23		32·8
Early dumping	12		17·1
Mild		9	
Moderate		3	
Severe		0	
Heartburn	4		5·7
Gastric or abdominal discomfort	4		5·7
Persistent loss of weight	3		4·3
Ulcer recurrence	0		0·0

Table III: SEVERITY AND TYPE OF DIARRHOEA

Type	Prepyloric antrectomy (% of 52 cases)	Vagotomy and prepyloric antrectomy (% of 18 cases)
Mild episodic	13·4	27·7
Mild continuous	0·0	5·5
Moderate episodic	0·0	5·5
Severe	0·0	0·0
Total	13·4	38·7

Table IV: OVERALL GRADING OF CLINICAL RESULTS IN 70 PATIENTS

Visick grade	No. of cases	%	
1. Excellent	47	67·1	89·9
2. Very good	16	22·8	
3. Satisfactory	6	8·6	
4. Unsatisfactory	1	1·4	

persistent loss of weight of between 6 and 8 kg, which, together with dyspeptic symptoms, caused their inclusion in the third group. The 3 led a normal working life, however, with few alimentary restrictions, and they concluded that the result of the operation was satisfactory.

Finally, none of the patients showed symptoms indicative of a possible recurrence.

Intestinal function

In this series special attention was paid to the manifestations of diarrhoea, the intensity and frequency of which are summarized in *Table III*.

After simple prepyloric antrectomy the incidence of diarrhoea was 13·4 per cent and when antrectomy was combined with vagotomy it was 38·7 per cent. It is necessary to point out that in most patients the diarrhoea was not a complaint, it was only recorded as the result of direct questioning of the patient. Relative urgency of defaecation was noted in some patients of both groups, but was more intense and frequent in those who had had a vagotomy.

Overall grading of clinical results

For this evaluation we adopted the classification of Goligher et al. (1968). Patients were placed in one of four groups according to the reviewer's estimation at the time of follow-up or questionnaire review (*Table IV*).

In group 1, as well as patients with no symptoms, there are 23 patients with milk intolerance as their only symptom and 3 others with very infrequent (three or four attacks per year), mild, episodic diarrhoea.

The most important symptoms in patients in group 2 were diarrhoea, dumping and abdominal discomfort of the mild type. In group 3 the symptoms were moderate dumping or diarrhoea, gastrointestinal discomfort and vomiting.

The only case in group 4 was a patient with peptic oesophagitis and stenosis. After a second operation with a favourable result he could be reclassified into group 3.

Discussion

Most surgical textbooks affirm the favourable results obtained in the surgical treatment of gastric ulcer by means of partial gastrectomy. However, the term 'partial gastrectomy' is ambiguous, because it can include a limited antrectomy on the one hand or a two-thirds or subtotal gastrectomy on the other. It would seem that, independent of the extent of the excision, the postoperative presentation of a recurrence is extremely rare. This implies that one might well question the need for an extensive resection. If one accepts that the appearance of adverse symptoms is in part proportional to the magnitude of the resection (Desmond, 1976), one can understand the importance of conserving the largest possible part of the gastric remnant.

If one accepts that an important cause of the pathogenesis of a gastric ulcer may lie in the hyperfunction of the antrum (Dragstedt, 1953) and that this, in turn, may be derived from or related to difficult antral emptying (Burge, 1964), it is logical to ask if the classic excision of a large part of the stomach is necessary. On the contrary, one could ask if it would be sufficient to limit the excision to the antrum itself, or even to the distal part, which is the principal site of the pathogenic lesions described by Burge (1964).

Previously published observations (de Miguel, 1970) showed that 76 per cent of patients operated on for gastric ulcer had antropyloric abnormalities leading, in many cases, to a distortion and narrowing of the pyloric canal with difficulties in gastric emptying as seen radiologically. In the present series the incidence of observed antropyloric abnormalities was similar (57, 72 per cent). It must be explained, however, why in 20 per cent of pati lesions were not observed.

Of the 79 patients included in this study, 19 had signs of scarring from a previous duodenal ulcer (only 1 showed an active ulcer). These 19 patients were submitted to a vagotomy also, with the idea of avoiding the possible risk of recurrence in the region of the gastroduodenal anastomosis. With a relatively short follow-up—only 25 patients have been followed for more than 5 years—it is not possible to assess the long term curative value of this operation, but the absence of any recurrence so far gives rise to optimism.

The assessment of the frequency and severity of diarrhoea was made after a thorough and searching interview in which even the most trivial and transient episodes of diarrhoea were noted. This may explain the incidence of 13·4 per cent after antrectomy alone. Using the same criteria, the incidence of 38·7 per cent when truncal vagotomy is included supports the view that postoperative diarrhoea is more dependent on parasympathetic denervation than on loss of the pylorus.

Other postoperative symptoms, when present, were usually very mild; for this reason clinical results were considered excellent or very good in 90 per cent of patients. One aspect which was notable at the final review was the good nutritional condition of the majority of the patients. Only the one patient suffering from postoperative oesophageal stenosis had to be considered a surgical failure (group 4). The low failure rate of 1·4 per cent after this operation must be accepted with some reservations until a longer period of observation has elapsed.

References

BURGE H. (1964) *Vagotomy*. London, Arnold, pp. 151–186.

DESMOND A. M. (1976) Trial and error in gastric surgery. *Proc. R. Soc. Med.* **69**, 257–262.

DRAGSTEDT L. R. (1953) Is gastric ulcer due to hyperfunction or dysfunction of the gastric antrum? *Surg. Gynecol. Obstet.* **97**, 517–519.

GOLIGHER J. C., PULVERTAFT C. N., DE DOMBAL F. T. et al. (1968) Five to eight-year result of Leeds–York controlled trial of selective surgery for duodenal ulcer. *Br. Med. J.* **2**, 781–787

DE MIGUEL J. (1970) Selective vagotomy and pyloroplasty in the treatment of gastric ulceration: some clinical observations and results. *Br. J. Surg.* **57**, 338–343.

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Colour lymphography in clinical surgery

D. J. LEAPER, MARY EVANS AND A. V. POLLOCK*

SUMMARY

In 38 patients undergoing femoral artery profundaplasty and in 18 having simple mastectomy with pectoral node biopsy, a 6·2 per cent solution of sodium sulphan blue was injected peripherally to outline the lymph nodes in the groin or axilla. Nodes and vessels were easily seen and the technique is now in routine use.

> Even though abundantly present, [the lymphatics] are often obscured by fat or are overlooked if not at the moment filled with fluid.
>
> RUDBECK (1653)

THE first half of the seventeenth century saw not only Harvey's discovery of the circulation of the blood but also the recognition of the nature of the lymphatic system. Gasparo Aselli first demonstrated lacteals in the mesentery of a recently fed dog in 1622 and, within a generation, lymphatic vessels had been discovered in nearly all parts of the body. During the eighteenth century William Hunter injected dyes into the lymph vessels of cadavers and was probably the first person to recognize their absorptive function (Leeds, 1977).

Since then the anatomy and physiology of the lymphatic system have been extensively investigated, but it was not until 1952 that *in vivo* lymphography was introduced by Kinmonth (1952, 1954), who pioneered both visual and X-ray lymphography using Patent Blue V and diodone, the latter subsequently being replaced by iodized poppy-seed oil (Lipiodol).

During the past 25 years, X-ray lymphography has been widely used for the investigation of lymphoedema (Kinmonth, 1972) and identification of abdominal node involvement in cancer and reticulosis (Wallace et al., 1977). It has also been used in combination with colour lymphography to outline nodes in the lower abdomen during radical hysterectomy for carcinoma of the cervix uteri, radiography being used to make sure that none was missed (Dahle, 1964; Hartgill, 1971). However, the possibility of using colour lymphography alone as an aid to the identification of lymphatic structures during operation was not realized until recently.

Vascular operations in the groin may be complicated by lymph fistulas or cysts due to unrecognized division of vessels and nodes and, at the suggestion of Mr C. V. Ruckley, we injected a blue dye peripherally to delineate these structures. Subsequently we realized that pectoral/axillary nodes could be more easily removed for biopsy if they were stained blue, and we thus adopted colour lymphography in patients undergoing mastectomy for carcinoma.

Patients and methods

The technique has been used in 38 patients undergoing femoral profundaplasty and in 18 having simple mastectomy with node biopsy. An ampoule of Disulphine Blue (Imperial Chemical Industries Ltd) is mixed with an equal quantity of 2 per cent lignocaine. For the demonstration of groin lymphatics (*Fig.* 1) 2 ml of the mixture are injected subcutaneously through a 25-gauge needle in aliquots of about 0·5 ml into the webs between the toes on the affected side (avoiding areas of gangrene). Two hours later a vertical groin incision is made and the blue lymphatics and nodes are easily avoided, ligated or sealed with surgical diathermy.

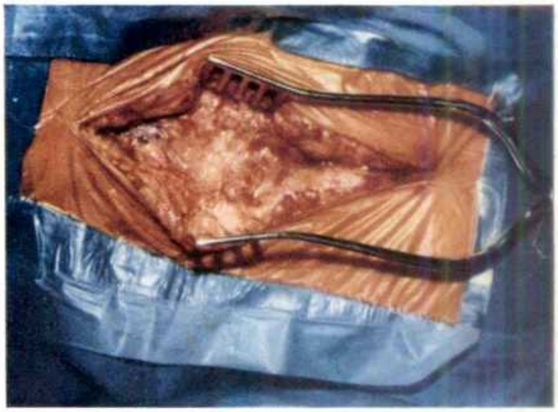

Fig. 1. Right groin dissection showing blue-coloured lymph vessels and nodes.

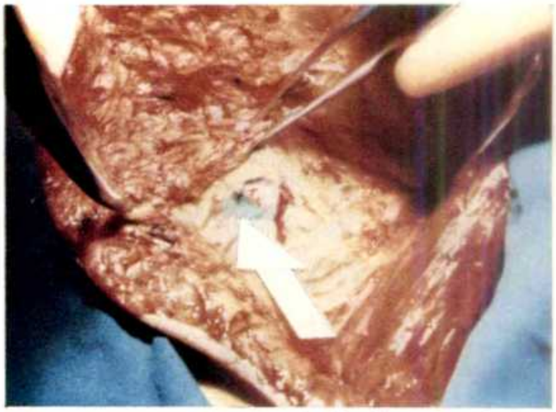

Fig. 2. Right axillary dissection showing blue-coloured nodes.

For simple mastectomy with pectoral and axillary node biopsy (*Fig.* 2), 2 ml of the same mixture are injected subcutaneously beneath the areola 2 h before operation.

Results

In the 38 patients having incisions for exposure of the upper femoral arteries, blue-coloured lymph vessels and nodes were found and no patient subsequently developed a lymph cyst or fistula. In the 18 patients undergoing mastectomy, coloured nodes were found in all but 1 (in whom the nodes were completely replaced by cancer).

Within 2 h of injection the patients' skin turned pale blue and their facies worried anaesthetists unaccustomed to the technique. The patients remained blue (and passed green urine) for a day or so and local staining of the interdigital clefts often persisted for a month or two.

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Apart from the colour changes, no adverse reactions to the injections were noted and the patients reported that they were not painful.

Discussion

Nadjafi and Vollmar (1976) overcame the problem of lymph fistulas after vascular operations in the groin by placing the skin and fascial incisions well lateral to the femoral arteries and reflecting the tissues medially. If, however, the lymphatics can be seen during operation, this precaution is unnecessary.

Simple mastectomy with pectoral and axillary node biopsy is widely advocated for the treatment of carcinoma of the breast. Even in the best hands, however, nodes were not found in 17 per cent of 124 patients (Forrest et al., 1976). Turner-Warwick (1958, 1959) developed intravital techniques for the demonstration of breast and axillary lymphatics, and in the small series reported here, the fact that the nodes were stained blue was a considerable help to the surgeon.

Kett, Varga and Lukács (1970) succeeded in cannulating breast lymphatics and produced X-ray lymphograms of 88 patients. These authors found that the first node to be filled was the pectoral and from there the Lipiodol spread to a mean of 15 nodes in the axilla and supraclavicular region. Secondary carcinoma could be recognized as filling defects in the nodes, but (as in our experience) when completely replaced by cancer, they did not take up the contrast medium.

Dyes

Many dyes are absorbed from the subcutaneous tissues by the lymphatics, including Evans Blue, Direct Sky Blue and Patent Blue V (Threefoot, 1960).

Patent Blue V (Sigma) is an 11 per cent solution of the sodium salt of sulphan blue with a molecular weight of 567 and a colour index of 42045 and is widely used to identify lymph vessels in the foot before their cannulation and injection with Lipiodol for X-ray lymphography. Disulphine Blue (ICI) is a 6·2 per cent solution of the same dye and was first introduced for the assessment (after intravenous injection) of skin viability in burns (Tempest, 1960).

These dyes differ from the Patent Blue V distributed by May & Baker Ltd for Laboratoire André Guerbet, which is a 2·5 per cent solution of a calcium salt of sulphan blue with a molecular weight of 1159 and a colour index of 42051.

In the few patients (not reported here) in whom we used Patent Blue V instead of Disulphine Blue we were disappointed by the results, and in two patients the lymphatics were not coloured.

Conclusion

The use of colour lymphography is valuable in operations on the femoral artery and in those for carcinoma of the breast, and it may have applications in other branches of surgery.

Acknowledgement

Our grateful thanks go to Professor J. B. Kinmonth for his most helpful comments and criticisms.

References

DAHLE T. (1964) Carcinoma cervicis uteri. *Acta Obstet. Gynecol. Scand.* **43**, Suppl. 7, 79–83.

FORREST A. P. M., ROBERTS M. M., CANT E. et al. (1976) Simple mastectomy and pectoral node biopsy. *Br. J. Surg.* **63**, 569–575.

HARTGILL J. C. (1971) Lymphogram control during pelvic lymphadenectomy. *Proc. R. Soc. Med.* **64**, 401–403.

KETT K., VARGA G. and LUKÁCS L. (1970) Direct lymphography of the breast. *Lymphology* **3**, 3–12.

KINMONTH J. B. (1952) Lymphangiography in man. A method of outlining lymphatic trunks at operation. *Clin. Sci.* **11**, 13–20.

KINMONTH J. B. (1954) Lymphangiography in clinical surgery and particularly in the treatment of lymphoedema. *Ann. R. Coll. Surg. Engl.* **15**, 300–315.

KINMONTH J. B. (1972) *The Lymphatics: Diseases, Lymphography and Surgery*. London, Arnold.

LEEDS S. E. (1977) Three centuries of history of the lymphatic system. *Surg. Gynecol. Obstet.* **144**, 927–934.

NADJAFI A. S. and VOLLMAR J. (1976) Indikatorische und technische Fehler als Ursache postoperativer Komplikationen in der Arterienchirurgie. *Helv. Chir. Acta* **43**, 97–102.

TEMPEST M. N. (1960) The use of intravenous dye technique in the assessment of tissue viability. *J. Bone Joint Surg.* **42B**, 646.

THREEFOOT S. A. (1960) Some chemical, physical and biologic characteristics of dyes used to visualise lymphatics. *J. Appl. Physiol.* **15**, 925–928.

TURNER-WARWICK R. T. (1958) The lymphatics of the breast. *Br. J. Surg.* **46**, 574–582.

TURNER-WARWICK R. T. (1959) Intravital techniques for the demonstration of lymphatics. *Ann. R. Coll. Surg. Engl.* **24**, 101–109.

WALLACE S., JING B.-S. and ZORNOZA J. (1977) Lymphangiography in the determination of the extent of metastatic carcinoma. *Cancer* **39**, Suppl. 1, 706–718.

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The stripping of varicose veins: a clinical trial of intermittent compression dressings

D. G. MELROSE, M. T. N. KNIGHT AND E. SIMANDL*

SUMMARY

This study compares a standard method of care for patients following excision and ligation of varicose veins with a new regimen which involves intermittent compression dressings. In a fully randomized between-patient prospective trial it has been found that the use of such dressings results in a significant reduction in post-operative pain and in the length of hospitalization and indicates that such dressings may improve the healing of surgical wounds.

INTERMITTENT compression devices have been used successfully in the conservative treatment of lymphoedema whether essential, traumatic or congenital (Pflug and Melrose, 1976) and in prophylaxis against postoperative deep vein thrombosis (Hills et al., 1972; Clark et al., 1974). Initially this prophylactic action was attributed to mechanically induced changes in venous flow in the femoral and calf veins (Calnan et al., 1970). However, Allenby and colleagues (1973) showed that an action of these devices was to enhance systemic levels of circulating fibrinolytic activity following operation, and Knight and Dawson (1976) showed that, even when applied to the arms, this systemic fibrinolytic enhancement was sufficient to reduce the incidence of deep vein thrombosis in the legs despite the likelihood of venous stasis. These findings suggested a more complex action for intermittent compression, and we were interested when Pflug (1974) reported that intermittent compression had reduced pain and oedema in a number of wounds in an uncontrolled study of several surgical procedures. We have followed up this interesting observation and have set up an international, multicentre, prospective, controlled, matched series of clinical trials to evaluate this effect of intermittent compression dressings on several varieties of surgical wound. In this report we have evaluated the effect of these dressings on wounds incurred in the stripping of the long or short saphenous vein combined with multiple ligations of incompetent perforators. In particular, this matched study has assessed the degree of pain, wound oedema and haematoma formation, blood loss, the incidence of wound infection and the rate of patient rehabilitation during the postoperative period in patients with and without intermittent compression of their wounds. The results give considerable cause for optimism that intermittent compression dressings will greatly improve the healing of surgical wounds.

Materials and methods

Intermittent compression dressing

The intermittent compression dressing is cyclically inflated with air from an electric pump, which can be easily suspended from the operating table or the bed of the patient. Each pump can operate two dressings at the same time from separate output ports. The 4-min cycle is equally divided into inflation and deflation with a 15-s changeover period. The inflation is held at a plateau pressure once the required pressure is reached. The maximum pressure within the compression device is selected from a range of 20–80 mmHg by means of a simple knob and adjusted by the patient to achieve maximum pressure compatible with comfort for that individual.

All the compression dressings used in the multicentre trial have been modified from a basic tubular model to meet the requirements of the individual specialties. The basic model consists of an outer fabric coat with a more pliable inner coat that is specially laminated to allow water transpiration at the molecular level whilst remaining impermeable to air and bacteria. In this study the dressing extends from the upper thigh to beyond the toes and has an open lower end for easy visualization of the circulation of the foot. A safety valve has been fitted for rapid deflation and a zip has been fitted to increase the ease with which the dressing can be applied.

Trial design

The trial was constructed as a fully randomized between-patient prospective trial providing a considerable excess of untreated patients. This bias has allowed the statistical analysis of the results after retrospective matching of the patients based on their height, weight, age and type of operation, the presence of incompetent perforating veins or gravitational oedema or a history of previous sclerotherapy, of varicose ulceration, of recurrent superficial thrombophlebitis or of previous operations on the veins of the lower leg. No age limit was placed on patients included in the trial. Patients with diabetes mellitus, the post-phlebitic syndrome, cardiac failure, liver failure or renal failure, those with drug idiosyncrasy or those who had received radiotherapy to the operation site were excluded. Patients with very severe ulceration or oedema were excluded from the trial also.

Operative technique

The following operative technique was used and all operations were carried out by one of the authors (E.S.). The limb was prepared with 0·5 per cent Hibitane in spirit. Incisions over either the groin or the popliteal fossa and the medial or lateral malleolus were made. Proximal stripping of the vessel was arrested at the points of entry of incompetent perforators or varicose tributaries. Separate incisions were made at these points and perforators and tributaries dissected and individually ligated. At the saphenofemoral junction the long saphenous vein was flush tied at the femoral vein; the popliteal fascia was then divided and the short saphenous vein ligated at the point of junction with the popliteal vein or, if it did not join, was followed into the thigh subfascially. After the long saphenous vein had been removed, clot was expressed from the long saphenous channel using a gauze pad as a roller. 4/0 braided cotton was used for loose closure of skin wounds on the leg and in all locations. The wounds were covered with simple gauze dressings.

Control cases had 2 × 6 in crêpe bandages applied from the toes to the upper thigh and were returned to the ward with the foot elevated on two pillows. Treated patients had the compression dressing applied directly over similar dressings. On return to the ward the dressing was connected to the pump and inflation commenced at setting 2. This setting was increased by the patient to the maximum pressure consistent with comfort. Inflation was continued for 10 days for 4 h twice a day. The dressing was removed for periods of exercise, ambulation, ablution and when the patient required a short respite from treatment. Mobilization of both groups was encouraged on the first postoperative day.

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Table I: COMPARISON OF VITAL STATISTICS AND RELEVANT PREOPERATIVE FEATURES OF THE CONTROL AND TREATED GROUPS

	Control	Treated
Height (cm)	164·8 s.d. 2·1	164·9 s.d. 2·2
Weight (kg)	67·4 s.d. 9·6	64·3 s.d. 8·9
Age (yr)	40·0 s.d. 8·7	42·4 s.d. 8·2
Sex (M/F)	2/23	1/24
Previous sclerotherapy	4/21	6/19
Incompetence of saphenofemoral junction	25/25	24/25
Incompetent perforators	25/25	25/25
Previous ulceration	3/22	3/22
Recurrent thrombophlebitis	8/17	7/18
Previous operation	2/23	2/23

Table II: COMPARISON OF THE NUMBER OF PATIENTS WITH MILD OR MODERATE DRESSING SATURATION (GRADE 1 OR 2) IN THE CONTROL AND TREATED GROUPS AT THE END OF THE OPERATION DAY AND ON THE NEXT 4 DAYS FOLLOWING OPERATION

	Day									
	Operation		1		2		3		4	
	1	2	1	2	1	2	1	2	1	2
Control	3	0	13	2	8	4	1	0	1	0
Treated	2	5	4	7	5	2	2	0	0	0

Table III: COMPARISON OF THE NUMBER OF UNITS OF PAIN ACCUMULATED BY EACH GROUP OVER THE FIRST 7 POSTOPERATIVE DAYS FOR EACH OBSERVER

	Surgeon	Physiotherapist	Patient
Control	13·2 s.d. 3·2	23·1 s.d. 6·0	34·1 s.d. 9·5
Treated	6·8 s.d. 3·2	12·5 s.d. 5·6	17·2 s.d. 8·0
	$P<0{\cdot}001$	$P<0{\cdot}001$	$P<0{\cdot}001$

Table IV: COMPARISON OF THE NUMBER OF PATIENTS WITH GRADES NIL, 1 OR 2 OEDEMA IN BOTH GROUPS ASSESSED ON THE FIFTH DAY FOLLOWING OPERATION

	Preop.		Postop.	
Grade	Control	Treated	Control	Treated
Nil	4	4	17	24
1	19	17	5	1
2	2	4	3	0

Table V: NUMBERS OF PATIENTS WHO WERE WALKING WITHOUT PAIN AND WITHOUT A LIMP ON EACH DAY FOLLOWING OPERATION FOR EACH GROUP

	Day									
	1	2	3	4	5	6	7	8	9	10
Control	0	3	9	17	19	19	22	23	23	25
Treated	2	5	21	23	24	25	—	—	—	—
					$P<0{\cdot}5$					

Postoperative study of wounds

The assessment of the wound was scored by a given observer throughout the trial. The saturation of wound dressings was assessed daily for the first 4 days following operation and recorded on a scale: nil, 1 and 2 representing no saturation, mild or moderate saturation respectively. The presence and time of onset of a wound discharge were noted and its serous, serosanguinous or purulent nature recorded and the discharge submitted for culture. The presence of a haematoma on the fifth postoperative day was assessed and recorded on a scale: nil, 1, 2 or 3 representing the absence or the presence of a mild, moderate or severe haematoma. The degree of oedema of the leg was assessed preoperatively and on the fifth postoperative day on a scale: nil, 1, 2 or 3 representing no oedema, or mild, moderate or severe oedema.

Mobilization was divided into the following stages: walking with support, walking unaided but with a limp and normal locomotion. The time at which each stage was reached was recorded for each patient.

In this study patients remained in hospital for a fixed length of time in order to complete the study and to avoid and correct complications.

Statistical analysis

A points system has been devised to match patients with similar preoperative clinical features in order that a comparison of their postoperative course might more accurately reflect the influence of the intermittent compression dressing. The nature, findings, extent and duration of the operation and the number of incompetent perforating vessels were precisely matched for each pair. A pair was considered to be matched if the remaining dissimilarities between them did not exceed 5 points. Three points were awarded to the pair if either of the following clinical features occurred in only one member of a pair: a history of previous sclerotherapy, previous operations, previous ulceration, recurrent thrombophlebitis or the presence of an incompetent saphenofemoral junction. A single point was awarded to every 3 kg of weight difference between members of a pair and a point for every difference of 5 in. in height between members of a pair. Patients were allocated to the age groups of 25 years and below and increasing decades beyond this age. A point was awarded for each decade of difference between members of the pair. A point was awarded for a difference of one grade of oedema. A difference of more than one grade nullified the pair.

Unless otherwise stated, the statistical significance of the data derived from the matched pairs was analysed using MacNemar's test incorporating a continuity correction.

Using the above system of retrospective matching, 25 pairs out of 87 patients accumulated 5 points or less (*Table I*). No patient of a pair was included more than once. Three control patients were not included in the total of 87 because intermittent compression was used in the later postoperative period to contain postoperative oedema.

Results

Blood loss

In *Table II* the number of patients with mild or moderate dressing saturation (grade 1 ± 2) during the postoperative period is compared. On the day of the operation and on the first postoperative day there was a greater degree of dressing saturation in the treated group. There was also a significantly greater number of patients with moderate dressing saturation on the operation day and on the first postoperative day. Throughout the remainder of the postoperative period there was no significant difference in the amount of blood expressed from the wounds of the two groups.

Pain

Pain was graded nil, 1, 2, 3 or 4, classified as no spontaneous pain, slight easily tolerated pain, moderate or bothersome pain, considerable pain and agony, respectively. Pain was independently assessed by the surgeon daily, by the physiotherapist twice a day and by the patient three times a day for 7 days following operation. The total amount of pain suffered by each group, recorded by each observer and by the patient, is shown in *Table III*. This is expressed as numbers of units of pain accumulated. The treated group suffered approximately half the pain recorded for the control group and the pain lasted for a shorter period of time. This difference was highly significant ($P<0{\cdot}001$). Analgesics were confined to pethidine and aspirin and

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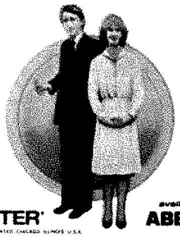

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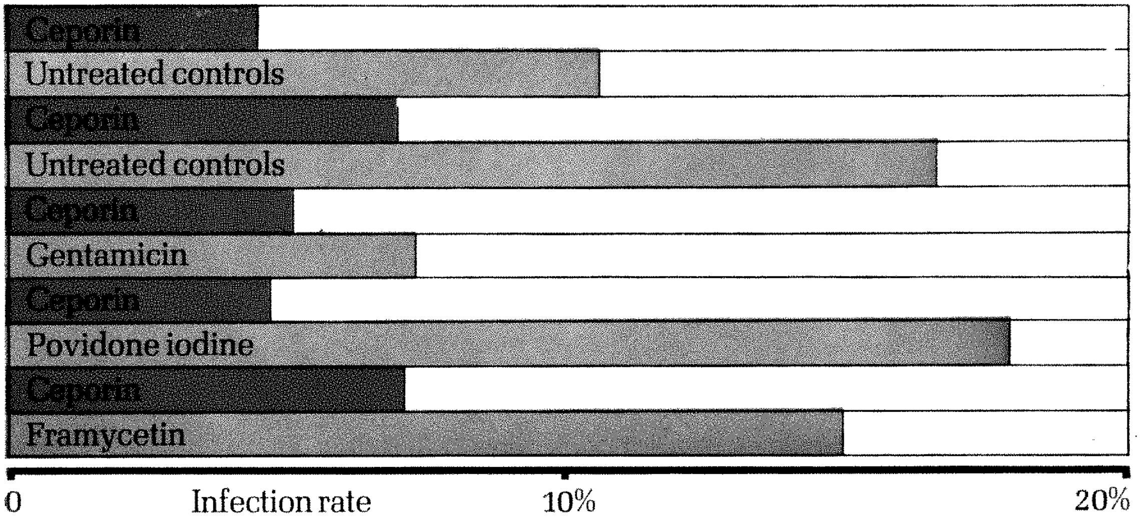
1. *Journal of Antimicrobial Chemotherapy* (1975) **1,** (Suppl.) 71
2. *Lancet* (1975) **4,** 1251



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the amount administered during the postoperative period was recorded. Whilst there was no significant difference in the requirement for pethidine administered routinely immediately following operation, the requirement for aspirin analgesia by patients in the treated group was significantly reduced.

Oedema and haematoma formation

Table IV compares the number of patients with grades nil, 1 or 2 oedema in both groups following operation and relates them to the preoperative findings. The incidence of postoperative oedema of grades 1 and 2 in the two groups shows a significant reduction in the treated group ($P<0{\cdot}5$). No significant difference was found between the two groups with regard to haematomas, although the majority of patients in the treated group were found to have no haematoma whilst the majority of patients in the control group had some haematoma formation. No wound infection occurred in either group.

Mobilization

From *Table V* it can be seen that a significantly higher proportion of the treated patients was fully mobilized, pain-free and ready for discharge on the third postoperative day ($P<0{\cdot}5$). By the end of the third postoperative day the treated group required a total of 47 days in hospital compared with the 63 days of the control group, i.e. a saving of 41 per cent. By the tenth day after operation the treated group had required 50 days of admission whilst the control group had required 95 days, i.e. a saving of 47 per cent.

Side effects of treatment

As expected, patients differed in their reaction to the new dressing technique, but apart from mild local sweating and occasional mild discomfort there were no important side effects or contraindications.

Discussion

This study indicates that the intermittent compression dressing has certain advantages over the standard method of postoperative care used at present following excision and ligation of varicose veins. The benefits may be divided into those of economy and those relating to improved patient care.

This device resulted in a reduced intake of analgesia in the treated group with a consequent saving on the bill for drugs. More importantly, there was a 41 per cent reduction in the hospitalization time before the patients reached a state of full mobilization. This effect was not limited to patients whose postoperative course could be expected to be short. This enhancement of mobilization has two effects; first, to return patients to the comfort of their homes more quickly, and secondly, to speed up patient turnover rates with consequent saving on inpatient service costs.

Of greater importance is that the intermittent compression dressing appears to have several valuable clinical attributes. It has resulted in a highly significant halving in the postoperative pain experienced by the patients and observed by several medical observers, and further contributed to the postoperative wellbeing of the patient by causing a significant reduction in postoperative oedema of the limb and wound. This study has also shown certain trends that are not amenable to statistical analysis because the number of cases examined was too small. These trends include a reduction in the amount of clinically discernible haematoma formation in the treatment group associated with the enhancement in the expression of collections from within the wound.

This novel method of dressing wounds would appear to have fulfilled some of the theoretical precepts upon which the dressings were devised. Both intermittent compression and static crêpe bandaging markedly reduced the oedema that was detected preoperatively, but the device also produced a reduction in postoperative limb oedema which was significantly greater than that achieved by crêpe bandaging alone. We suggest that the reduction in oedema and expression of collections may have resulted in a more rapid removal of the cellular breakdown products responsible for pain and thus resulted in increased patient comfort. Also, it may be that maintaining a more normal cellular environment near the wounds has allowed more rapid mobilization and rehabilitation to take place. In this small series no patient in either group suffered a wound infection and we therefore do not have evidence to suggest that the intermittent compression dressing leads to improved cellular nutrition and hence improved cellular resistance to infection.

Most of the patients wearing intermittent compression dressings did so without complaint. Some experienced mild sweating but there were no important side effects or contraindications and the absence of these, together with statistically significant evidence that the dressing promoted more rapid recovery after surgical treatment of varicose veins, encourages us to recommend this method of postoperative treatment.

Acknowledgements

This study has been made possible by grants from the Department of Health and Social Security to Professor D. G. Melrose and to Flowtron-Aire Ltd who provided the special equipment used. We would like to acknowledge the help of Miss R. Dawson and Miss M. Clay in the analysis of the large volume of data.

References

ALLENBY F., BOARDMAN L., PFLUG J. J. et al. (1973) Effects of external pneumatic intermittent compression on fibrinolysis in man. *Lancet* **2**, 1412–1414.

CALNAN J. S., PFLUG J. J. and MILLS C. (1970) Pneumatic intermittent-compression legging simulating calf-muscle pump. *Lancet* **2**, 502–503.

CLARK W. B., MCGREGOR A. B., PRESCOTT R. J. et al. (1974) Pneumatic compression of the calf and postoperative deep-vein thrombosis. *Lancet* **2**, 5–7.

HILLS N. H., PFLUG J. J., JEYASINGH K. et al. (1972) Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. *Br. Med. J.* **1**, 131–135.

KNIGHT M. T. N. and DAWSON R. (1976) Effect of intermittent compression of the arms on deep venous thrombosis in the legs. *Lancet* **2**, 1265–1267.

PFLUG J. J. (1974) Intermittent compression: a new principle in treatment of wounds? *Lancet* **2**, 355–356.

PFLUG J. J. and MELROSE D. G. (1976) Prevention of thromboembolic disease in surgery. *Vasa* **5**, 63–69.

SABRI S., ROBERTS V. C. and COTTON L. T. (1972) The effects of intermittently applied external pressure on the haemodynamics of the hind-limb in greyhound dogs. *Br. J. Surg.* **59**, 219–222.

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Internal fixation versus primary prosthetic replacement in acute femoral neck fractures: a prospective, randomized clinical study

ODD SÖREIDE, ANDERS MÖLSTER AND TOR STEINAR RAUGSTAD*

SUMMARY

A prospective, randomized clinical study has been performed on 104 patients with an acute femoral neck fracture, comparing internal fixation (von Bahr screws) with primary prosthetic replacement (Christiansen endoprosthesis). Immediate weight bearing was allowed in both groups.

The postoperative mortality rate was similar in the two groups.

Internal fixation proved to be a less time-consuming operation, gave a shorter hospitalization time and was associated with a significantly reduced morbidity rate compared with prosthetic replacement. No blood transfusion was needed in the internal fixation group.

Primary prosthetic replacement was associated with earlier postoperative mobilization, probably gave a more definitive treatment with fewer reoperations, and showed better results at 1-year follow-up.

ACUTE, displaced femoral neck fractures are traditionally treated by reduction and internal fixation. Various fixation devices have been constructed and used in the treatment of this fracture. The failure rate following internal fixation is very high, however, and is related to the fixation device only to a small degree.

The high incidence of early and late failure which follows internal fixation has prompted many surgeons to use primary prosthetic replacement instead in the treatment of these fractures. A review of published series shows a high complication and failure rate even with this method (Hunter, 1969; Lunt, 1971; Raine, 1973). With the introduction of bone cement and more refined techniques and prostheses, however, the morbidity and failure rates have declined rapidly.

Our experience with primary prosthetic replacement has been reported previously (Söreide et al., 1975). The results were favourable and in many respects comparable with those of internal fixation, with a low morbidity and mortality rate. However, there is no general agreement concerning the place of prosthetic replacement in the treatment of acute femoral neck fractures. Indeed, many authors state that a prosthesis is not indicated in poor risk patients and many of our patients with this fracture do come into this category. Similarly, the high morbidity and mortality rate and, especially, the very high infection rate in series reported by various authors seem prohibitive.

There are only a few series in the literature comparing prosthetic replacement with internal fixation and all of them are retrospective and non-randomized (Hunter, 1969; Raine, 1973; Hunter, 1974; Johnson and Crothers, 1975). The need for a prospective randomized clinical study was obvious. Therefore we started such a trial in October 1974, a study which we hoped would solve many of the disputed problems in the treatment of femoral neck fractures in the elderly patient.

The Christiansen trunnion bearing hip prosthesis and von Bahr internal fixation screws have been used.

Patients and methods

Clinical series

Selection of patients: From 1 October 1974 all patients over the age of 67 admitted to the surgical department with an acute femoral neck fracture (Garden type 2–4) were randomized into two groups according to their date of birth. At the end of September 1976 a total of 123 patients had been admitted. One of these patients had a pathological fracture (metastasis from breast carcinoma) and 16 other patients had been systematically, incorrectly randomized (in a period when the senior author was on a study leave). These 17 patients are excluded from this study. The remaining 104 patients, 53 in the prosthetic group and 51 in the internal fixation group, form the basis for this report.

Statistical analysis: In the statistical analysis of the results, the χ^2 test and Student's t test (two-tailed) have been used.

Age and sex distribution: The age and sex distribution are given in *Fig.* 1. The mean age was 78·3 years in the prosthetic group and 77·9 years in the internal fixation group. There is no statistical difference in the age distribution of the two groups nor in the sex distribution.

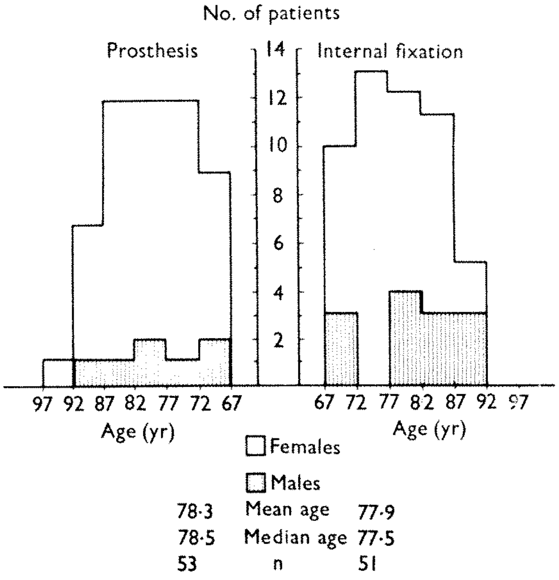

Fig. 1. Patient series: age and sex distribution.

Preoperative comparison

Great efforts were taken to evaluate the patients' preoperative general status to prevent later difficulties in interpretation of the results. The high frequency of concomitant disease found in all studies was confirmed. There was no statistical difference

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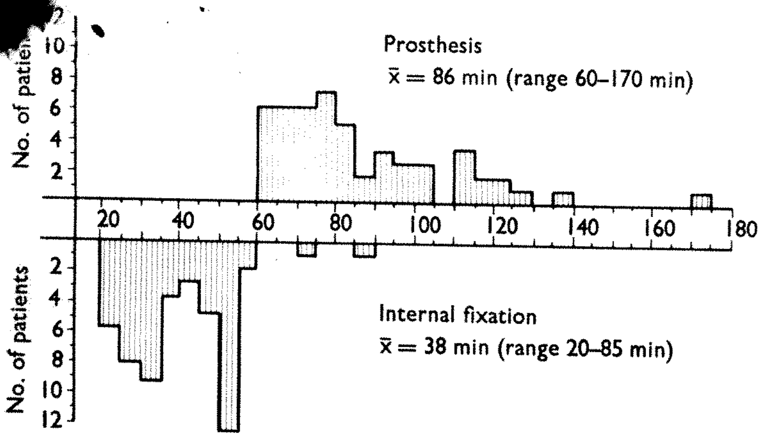

Fig. 2. Duration of the operation (the time needed for the reduction procedure is not included in the internal fixation group).

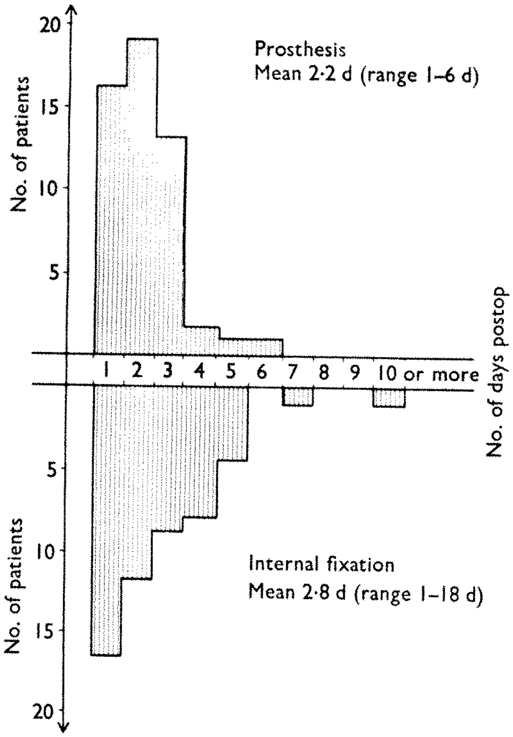

Fig. 3. Postoperative day of mobilization and weight bearing. (One patient in each group died before mobilization.)

between the internal fixation group and the prosthesis group when the frequency of concomitant disease was compared.

None of our patients was operated on as an emergency. The preoperative delay was similar in the two groups ($P > 0{\cdot}10$).

Treatment

All patients were treated by tibial traction on admission. Prophylactic anti-thrombosis therapy was started from the first day and concomitant diseases were treated if necessary. The operations were performed from 1 to 7 days later by different surgeons, as part of their surgical training.

Prosthesis group: Replacement arthroplasty was performed using a Christiansen trunnion bearing hip prosthesis. The technique has previously been described (Söreide et al., 1975). Immediate weight bearing was allowed. Penicillin and cloxacillin were administered to all patients, pre- per- and postoperatively (cephalosporins were given if penicillins were not tolerated).

Internal fixation group: The internal fixation was performed using von Bahr screws. The operative steps have been described by von Bahr et al. (1974) and Söreide et al. (1977). No antibiotics were given. Full weight bearing was started as soon as possible postoperatively.

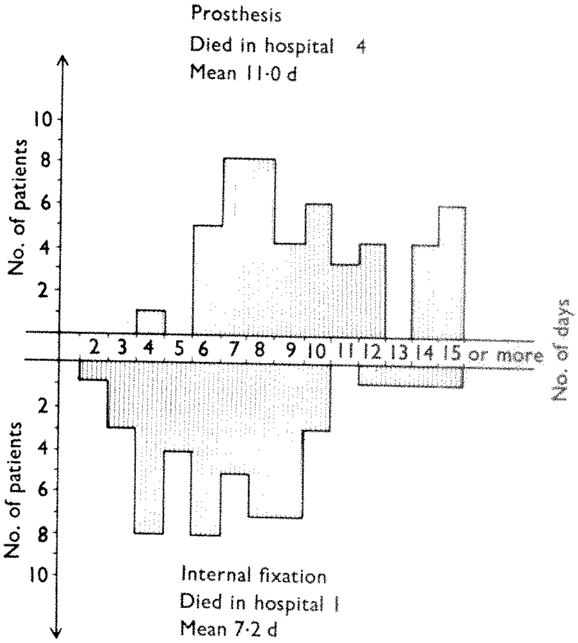

Fig. 4. Necessary time of hospitalization (for explanation *see* text).

Evaluation of the operative procedures

Duration of the operations: In the internal fixation group the mean operative time was 38 min (range 20–85 min) (*Fig.* 2). The time needed for the reduction procedure is not included. In the prosthesis group a mean operative time of 86 min was found (range 60–170 min) (*Fig.* 2). The operative time in the prosthesis group was significantly longer than in the internal fixation group ($P = 0{\cdot}005$).

Table I: WOUND COMPLICATIONS

	Prosthesis ($n = 53$)	Internal fixation ($n = 51$)
Superficial infection	3	2
Haematoma	1	3
None	48	46

The statistical difference between the groups is not significant.

Table II: GENERAL COMPLICATIONS

Complications	Prosthesis ($n = 53$)	Internal fixation ($n = 51$)
Thromboembolism	2*	0
Cardiopulmonary	3	1
Neurological	2	0
Drug exanthema	2	0
Urinary retention	3	2
None	42	48

* In one patient, more than one complication was recorded. The difference between the groups was statistically significant ($P = 0·04$).

Table III: MORTALITY RATES RECORDED POSTOPERATIVELY (FIRST MONTH), 6 MONTHS AND 1 YEAR AFTER THE OPERATION

	Prosthesis ($n = 53$)	Internal fixation ($n = 51$)
Peroperatively	0	0
First month	3 (5·7%)	3 (5·9%)
Six months	5 (9·4%)	6 (11·8%)
First year	11 (20·8%)	9 (19·6%)

The statistical difference between the groups is not significant.

Table IV: LOCAL COMPLICATIONS INDICATING FURTHER TREATMENT AT 1 YEAR AFTER THE INITIAL OPERATION

Group	Complication	No. of patients	Treatment	
			Op.	Con.
Prosthesis ($n = 53$)	Postoperative luxation	3	1	2
	Delerin luxation	2	2	—
Internal fixation ($n = 51$)	Mechanical failure	11	9	2
	Necrosis of femoral head	2	0	2

Op., Operative; Con., conservative.
Statistical difference: No. of patients, $P = 0·06$; Operative, $P = 0·06$; Conservative, n.s.

Blood loss: Blood transfusion was not needed in the internal fixation group. In the prosthesis group 18 of the 53 patients needed blood transfusion, totalling 19 000 ml (38 units) in all, which represents 358 ml per patient in the whole prosthesis group.

Mobilization and weight bearing: The first day of mobilization was recorded in both groups and is shown in *Fig.* 3. In the prosthesis group the mean time from operation to weight bearing was 2·2 days (range 1–6 days) compared with 2·8 days (range 1–18 days) in the internal fixation group. Using a one-way statistical analysis this difference is almost significant ($P = 0·06$). However, a larger series is necessary to reach a definite conclusion.

Duration of stay: Owing to the lack of long-stay geriatric hospitals, many patients stay in our hospital for a considerable time and thus the total hospitalization time is not a reliable index. We have recorded what we call the 'necessary hospitalization time', which means the time until the particular patient is walking with/without help, has no pyrexia and any post-operative complications have been treated. The necessary time of hospitalization is recorded in *Fig.* 4. The mean time for the internal fixation group was 7·2 days compared with 11 days in the prosthesis group. This difference is statistically signi[illegible] ($P = 0·01$).

Results

Early results

Morbidity: By this we mean all complications recorded in the first postoperative month which were not related to the fracture. The wound complications are listed in *Table I*. All infections in both groups were superficial and were successfully treated by antibiotics. Statistical analysis by χ^2 gave no significant difference between the groups.

The general complications experienced by our patients are shown in *Table II*. There were more complications in the prosthesis group than in the internal fixation group. This difference is statistically significant ($P = 0·04$) (χ^2 analysis).

Mortality: No patient in either group died during the operation. Mortality has been recorded 1, 6 and 12 months after the operation and the figures are shown in *Table III*. The difference in mortality rates is statistically not significant (χ^2 analysis).

Late results

The patients in the prosthesis group were followed up clinically as long as necessary. The patients in the internal fixation group were followed until healing of the fracture was complete or until failure (*see below*) had been treated. One year postoperatively all surviving patients were asked to come for a complete clinical examination and control radiograph. The mean follow-up period is 14·5 months (range 12–23 months) in the prosthesis group compared with a mean follow-up period of 14·7 months (range 12–24 months) in the internal fixation group. Thus the results obtained in each group can be compared.

Late complications: The late local complications for each group are listed in *Table IV*. In the prosthesis group postoperative luxation of the prosthesis developed in three patients. Analysis of the immediate postoperative radiographs showed that, in these patients, the prosthetic stem had been implanted in anteversion of varying degrees. Reoperation with removal of the prosthesis and implantation of a new stem in the correct position was necessary in one patient. For the other two a closed reposition procedure was performed.

The separation of the two components of the prosthetic head (here called delerin luxation), which only can occur with the Christiansen endoprosthesis,* has been reported previously from this hospital (Solhaug et al., 1976). In both our cases reoperation was necessary.

In the internal fixation group mechanical failure was found in 11 patients (22 per cent). In this context, mechanical failure means dislocation of the fracture with or without screw slippage. In 9 of these 11 patients prosthetic replacement has been performed. One patient is waiting for prosthetic replacement and in another patient reoperation is not indicated due to the patient's present general condition. Two patients presented with radiographical signs of avascular necrosis of the femoral head. No pseudarthrosis was found.

Statistical analysis (χ^2) indicated that the frequency of late complications in the internal fixation group

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* The design of the Christiansen endoprosthesis has now been changed in order to avoid this complication.

[illegible] probably higher than in the prosthesis group [illegible] = 0·06). Similarly, the need for a second operation was probably greater in the internal fixation group than in the prosthesis group ($P = 0{\cdot}06$).

Late infection: In one patient belonging to the prosthesis group deep infection occurred and the prosthesis had to be removed. We feel, however, that this case is not typical of the infection that is relevant in this discussion, which we hope to clarify with the patient's history.

Case report: An 89-year-old female patient in a mental hospital was admitted in June 1976 with an acute femoral neck fracture after a fall. According to randomization she received primary prosthetic replacement. There were no postoperative complications, particularly no infection.

After discharge she developed a flexion contracture in the operated hip and, in August 1976, bedsores over the trochanteric region. The prosthesis then luxated and soon became visible. Infection supervened and the prosthesis had to be removed.

For the purposes of this study, this patient has been classified as a failure.

Follow-up examination: Of the surviving patients, 5 in the prosthesis group and 2 in the internal fixation group were not examined because they had moved away from the area. Thus 36 patients in the prosthesis group and 31 patients in the internal fixation group were available for follow-up examination.

The ability to walk and the need for walking aids are recorded in *Table V*. There is no significant difference between the groups (analysis by χ^2).

Objective hip assessment was performed using Stinchfield's classification system (*Table VI*) and the results are given in *Table VII*. The 11 patients in the internal fixation group with primary mechanical failure have all been classified as poor. In the prosthesis group the patient with deep infection and one patient with an unsuccessfully repositioned dislocated prosthesis have also been recorded as poor. In the prosthesis group 30 out of 38 patients obtained the classification excellent or good, compared with 23 of the 42 patients in the internal fixation group.

When comparing the number of patients in each group classified as excellent or good with the number of patients in the two groups classified as fair and poor the results in the prosthesis group are significantly (χ^2) better than in the internal fixation group ($P = 0{\cdot}025$).

Range of movements in the operated hips: Two patients in the prosthesis group had a flexion contracture of 5° compared with 3 patients in the internal fixation group with contractures of 10°, 15° and 25° respectively. The range of movements in all the patients that were examined is shown in *Fig.* 5 (left hip turned). Statistical analysis revealed no difference between the groups.

Discussion

As shown in this paper, primary prosthetic replacement does not lead to increased postoperative mortality compared with internal fixation. This finding contrasts with the general view recently expressed by Garden (1977) and the findings in non-randomized groups of patients (Hunter, 1969; Lunt, 1971; Hunter 1974). The low mortality rate in the prosthetic group, however, is in good accordance with the results of a previous study of primary prosthetic replacement from this hospital (Söreide et al., 1975).

Table V: RESULTS OF FOLLOW-UP EXAMINATIONS

	Prosthesis ($n = 36$)	Internal fixation ($n = 31$)	P
*Walking ability**			
Unchanged	13	11	
Reduced	23	19	n.s.
No information	—	1	
Walking aids			
None	11	8	
Stick	16	15	
Crutches	5	3	n.s.
Wheelchair	2	5	
Bedridden	2	—	

* The patient's personal opinion.

Table VI: STINCHFIELD'S HIP ASSESSMENT SYSTEM (GRADING OF DISABILITY ACCORDING TO PAIN, MOVEMENT AND CAPACITY FOR WALKING)

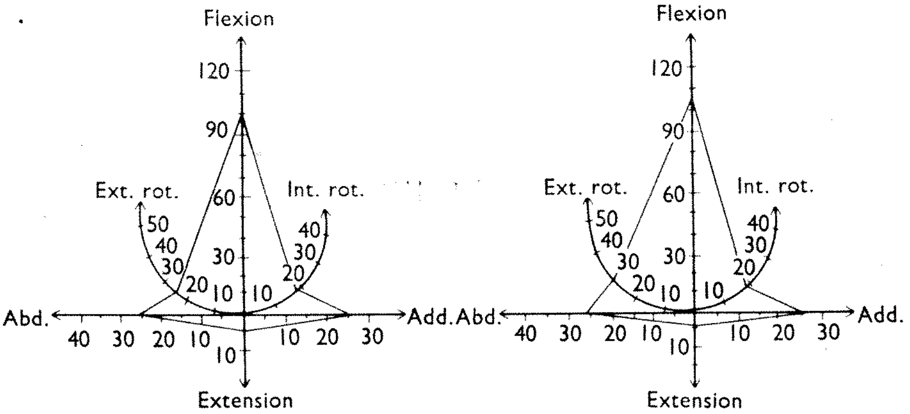
Pain	
Severe (loss of sleep)	1
Severe when walking, unable to work	2
Moderate (able to do light work)	3
Pain after effort (relieved by rest)	4
Slight and intermittent	5
Absent	6
Movement	
Fixed in bad position	1
Fixed in good position	2
0–70°	3
70–140°	4
140–200°	5
More than 200°	6
Walking	
Impossible or almost so	1
Short distances only	2
Restricted, e g. an hour with stick	3
Long distances with stick, short without	4
No stick, but limping	5
Normal	6
Classification	
Excellent	16 points or more
Good	12–15 points
Fair	9–11 points
Poor	8 points or less

Table VII: RESULTS OF THE FOLLOW-UP: OBJECTIVE HIP ASSESSMENT ACCORDING TO STINCHFIELD'S CLASSIFICATION SYSTEM

	Prosthesis ($n = 38$)	Internal fixation ($n = 42$)
Excellent	11	8
Good	19	15
Fair	5	7
Poor	3	12

The difference between the groups was statistically significant ($P = 0{\cdot}025$).

Primary prosthetic replacement, on the other hand, is followed by an increased morbidity rate compared with internal fixation. This finding corresponds well with those of other authors (Hunter, 1969; Raine, 1973; Hunter, 1974; Johnson and Crothers, 1975). This increase must reflect the difference in the magnitude of the two operative procedures, reflected in the increased operation time and the greater blood loss in the prosthetic group. Interestingly, the increased



Prosthesis

Internal fixation

Fig. 5. Range of movements in the operated hips according to Spangfort's scheme (left hip turned).

morbidity rate did not result in an increased mortality rate.

Both operations carry the risk of complications requiring secondary treatment. The reoperations in the prosthetic group follow luxation or loosening of the prosthetic stem, protrusion into the acetabulum or deep infection. Postoperative luxation can be avoided by careful peroperative technique as previously shown (Söreide et al., 1975). Protrusio acetabuli has not been a problem with the Christiansen endoprosthesis (Kavlie and Sundal, 1974; Söreide et al., 1975). The only serious threat to a good functional result is deep infection. Although the infection rate in this study can be said to be zero, previous experience (Söreide et al., 1975) and a literature survey clearly show that postoperative infection cannot be totally avoided. In the internal fixation group reoperations are needed owing to mechanical failure, non-union or necrosis of the femoral head. The frequency of these complications has been remarkably constant during the years (Öhman et al., 1969; Johnson and Crothers, 1975; Tillberg, 1976). Garden (1971, 1977) and Barnes et al. (1976) have presented convincing data showing that the complication rates can be reduced by better operative technique. This is in accordance with our findings (Söreide et al., 1979). From this study, however, it appears that primary prosthetic replacement offers the most definitive treatment.

We have shown that the results of 1-year follow-up examination are better in the prosthetic group than in the internal fixation group. However, the results of endoprosthetic replacement and of internal fixation *plus* later prosthetic replacement in the patients with mechanical failure, non-union on necrosis of the femoral head would probably be identical. However, the 'two-step' approach to the treatment of femoral neck fractures in the elderly puts a greater burden on the hospital's services and finances, and reoperations represent another threat to the life of these patients. The cost-effectiveness problem must also be considered when comparing these two types of treatment.

Acknowledgements

We would like to thank the former head of the Department of Traumatology and Orthopaedics, Professor Sven Olerud, whose inspiration and enthusiasm inspired this study. The statistical analysis was performed by Statistician Siri Nome Ekhom, of the Medical Faculty, University of Bergen.

References

VON BAHR V., SYK B. and WALHEIM G. (1974) Osteosynthesis of femoral neck fractures using screws. *Acta Chir. Scand.* **140**, 277–282.

BARNES R., BROWN J. T., GARDEN R. S. et al. (1976) Subcapital fractures of the femur. A prospective study. *J. Bone Joint Surg.* **58B**, 2–24.

GARDEN R. S. (1971) Malreduction and avascular necrosis in subcapital fractures of the femur. *J. Bone Joint Surg.* **53B**, 183–197.

GARDEN R. S. (1977) Selective surgery in medial fractures of the femoral neck: a review. *Injury* **9**, 5–7.

HUNTER G. A. (1969) A comparison of the use of internal fixation and prosthetic replacement for fresh fractures of the neck of the femur. *Br. J. Surg.* **56**, 229–232.

HUNTER G. A. (1974) A further comparison of the use of internal fixation and prosthetic replacement for fresh fractures of the neck of the femur. *Br. J. Surg.* **61**, 382–384.

JOHNSON J. T. H. and CROTHERS O. (1975) Nailing versus prosthesis for femoral neck fractures. *J. Bone Joint Surg.* **57A**, 686–692.

KAVLIE H. and SUNDAL B. (1974) Primary arthroplasty in femoral neck fractures. A review of 269 consecutive cases treated with the Christiansen endoprosthesis. *Acta Orthop. Scand.* **45**, 579–590.

LUNT H. R. W. (1971) The role of prosthetic replacement of the head of the femur as primary treatment for subcapital fractures. *Injury* **3**, 107–113.

ÖHMAN V., BJÖRKEGREN N. Å. and FAHLSTRÖM G. (1969) Fractures of the femoral neck. A five-year follow-up. *Acta Chir. Scand.* **135**, 27–42.

RAINE G. E. T. (1973) A comparison of internal fixation and prosthetic replacement for recent displaced subcapital fractures of the neck of the femur. *Injury* **5**, 25–30.

SOLHAUG J. H., MÖLSTER A. and SÖREIDE O. (1976) A new design of the Christiansen endoprosthesis. Report of two cases in which separation of the two components of the prosthetic head occurred. *Acta Orthop. Scand.* **47**, 415–418.

SÖREIDE O., LERNER A. P. and THUNOLD J. (1975) Primary prosthetic replacement in acute femoral neck fractures. *Injury* **6**, 286–293.

SÖREIDE O., MÖLSTER A. and RAUGSTAD T. S. (1977) Immediate weight-bearing after internal fixation of femoral neck fractures using von Bahr screws. Preliminary report of a prospective clinical trial. *Acta Orthop. Scand.* **48**, 659–664.

SÖREIDE O., MÖLSTER A. and RAUGSTAD T. S. et al. (1979) Internal fixation of fractures of the neck of the femur using von Bahr screws and allowing immediate weight bearing., *Injury* **10** (In the press.)

TILLBERG B. (1976) Treatment of fractures of the femoral neck by primary arthroplasty. *Acta Orthop. Scand.* **47**, 209–213.

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A 'universal' tube-holding device

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DURING medical and surgical practice there are many and varied occasions on which it is necessary to retain tubes in the patient for diagnostic and treatment purposes. The traditional way of doing so is to use an anchoring suture in the skin, strapping and bandaging. Either as an alternative or as a complement to these methods of retaining tubes, a device has been made available which is both convenient and effective and enables tube positions to be easily adjusted if required.

The device is made of plastic and is disposable. It consists of a base plate on which are mounted two flanges in parallel. The flanges bear a series of slots tailored to receive a variety of tubes, such as those used for infusion, transfusion, catheterization and drainage (*Fig.* 1).

In use, the device, supplied presterilized by ethylene oxide in a double-wrapped package, is stuck to the patient's skin by means of a double-sided plaster on the base plate. The tube to be retained is inserted into the flange slots of appropriate size so that it is gripped firmly, without obliterating its lumen, at two sites in a cleat action.

The purposes for which the 'universal' tube-retaining device can be used are intravenous infusion and transfusion; wound drainage by vacuum drains, suction sump drains and passive tube drains; common bile duct T tube drainage (*Fig.* 2); fistula suction (*Fig.* 3); ureteric catheterization for retrograde pyelography; cardiac and Seldinger arterial catheterization.

The device is available from Downs Surgical Ltd, Church Path, Mitcham, Surrey.

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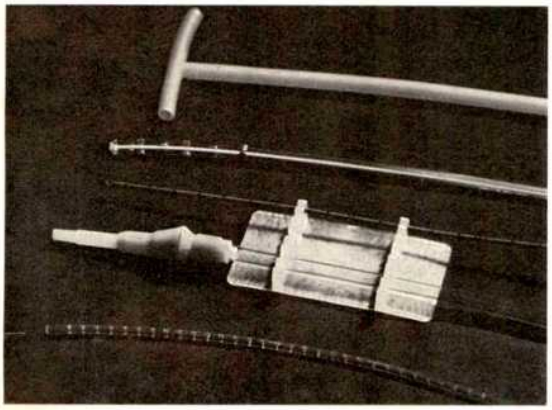

Fig. 1. The device can hold a variety of tubes.

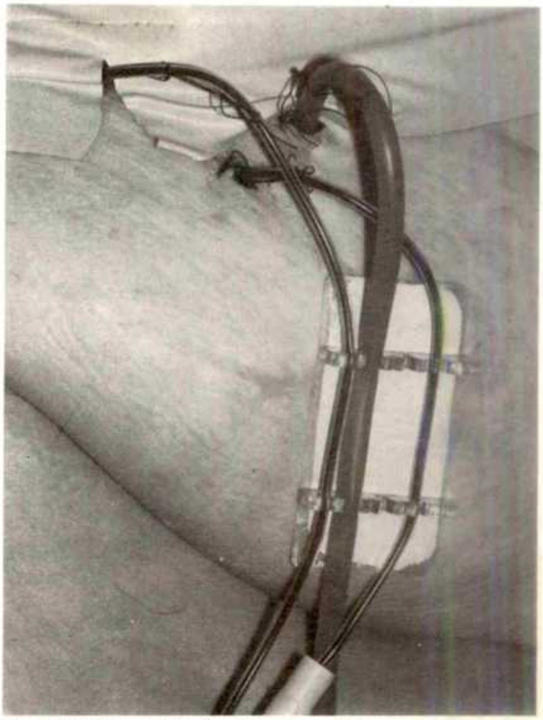

Fig. 2. Holding a bile duct T tube and two vacuum drainage tubes following biliary tract surgery.

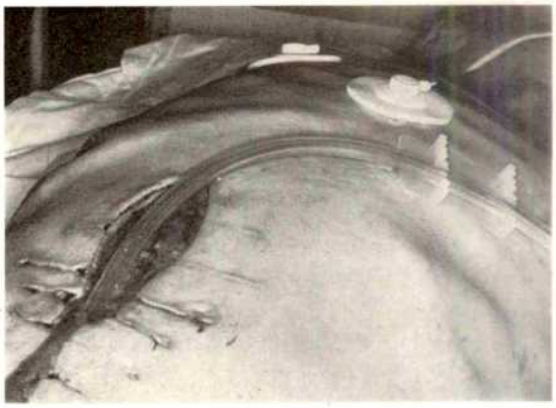

Fig. 3. Holding a suction sump drain to control a fistula.

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Splenectomy for undiagnosed splenomegaly

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SUMMARY

During the 9-year period 1968–76 116 splenectomies were performed at the General Hospital, Nottingham. Of these, 13 (11 per cent) were undertaken for unexplained splenomegaly. In 6 patients a diagnosis was established by the operative procedure (2 with sarcoidosis, 2 splenic cysts, 1 Gaucher's disease and 1 haemangiosarcoma). Histological examination of the excised spleens in the remaining 7 patients showed no specific features. Two of these patients benefited considerably from removal of very large spleens. Another patient died from lymphosarcoma which was diagnosed 21 months after splenectomy. In the remaining 4 patients with mild to moderate splenomegaly, there were no real diagnostic or therapeutic advantages. It is concluded that splenectomy should always be considered in patients with unexplained moderate or gross splenomegaly but it may not be helpful in the patient whose spleen is only mildly enlarged.

IN most patients living in temperate climates, the cause of an enlarged spleen is readily determined by clinical investigation. Even after careful evaluation, however, a small group of patients remains in which the cause of the splenomegaly is uncertain. Some of these patients appear to be in robust health whilst others are obviously ill. When non-invasive techniques have failed to reveal the cause of the splenic enlargement, splenectomy has to be considered.

Under these circumstances, the primary objective of splenectomy is positive pathological diagnosis. Additionally, there may be other secondary benefits, such as the cure of a hypersplenic state, the reduction of an expanded plasma volume or the removal of a large tumour which has become a painful and cumbersome burden. These advantages have to be set against the appreciable morbidity and mortality of splenectomy and the long term vulnerability to infection of the asplenic state (Ramsay and Bouskill, 1973). Unfortunately, there is the possibility that the excised splenic tissue may have no specific histological characteristics, leaving the clinician uncertain as to whether he is dealing with a benign disorder or a more sinister process, presaging a lymphomatous or leukaematous state.

The potentials of diagnostic splenectomy have been discussed in standard texts but there have been few detailed reports in recent years. Herman and his colleagues (1968) described 52 patients who underwent splenectomy for unexplained splenomegaly at the Cleveland Clinic during the preceding 10 years. Of these patients, more than half were found to be suffering from lymphoma or congestive splenomegaly and in only 1 case was the diagnosis still uncertain after splenectomy. Although other authors have reported groups of patients with specific diseases that were diagnosed at splenectomy (Hickling, 1964; DasGupta et al., 1965; Skarin et al., 1971), there have been no recent descriptions of the results of splenectomy for undiagnosed splenomegaly after full conventional investigations. This paper describes 13 such patients.

Patients and methods

The 13 patients whose clinical data are summarized in *Table I* formed part of a series of 116 splenectomies carried out at the General Hospital, Nottingham, during the period 1968–76. Of the 116 splenectomies, there were 21 associated with major upper abdominal surgery, 32 for traumatic or spontaneous rupture of the spleen, 17 for idiopathic thrombocytopenic purpura, 12 for various forms of haemolytic anaemia, 13 for lymphoma, 5 for chronic leukaemia and 3 for myelosclerosis. The remaining 13 cases were undiagnosed before splenectomy and are reported in this paper.

Each of the patients subjected to splenectomy for undiagnosed splenomegaly had had repeated peripheral blood film examinations and bone-marrow and/or trephine biopsies.

Blood from all patients was assessed for haemolysis by routine haematological methods. Measurements of red cell mass (RCM), splenic red cell pool (SRCP), red cell survival (RCS) and surface counting studies were also carried out in *Cases* 3, 4, 7, 8, 9 and 11, using ^{51}Cr-labelled erythrocytes as described earlier (Toghill and Green, 1975). Plasma volumes (PV) were measured using ^{125}I- or ^{131}I-labelled human albumin. The results of these investigations are shown in *Table II*. In only one patient (*Case* 11) was there evidence of frank haemolysis with excessive splenic uptake on surface counting. This patient's red cell survival (T_{50} ^{51}Cr) was reduced to 10 days (normal 24–28) and the splenic sequestration index increased to 250. This index was calculated as described by Parker et al. (1977), a value of greater than 100 indicating moderate to severe red cell destruction in the spleen (Jandl et al., 1956).

All patients had routine liver function tests performed and all had liver biopsies except *Cases* 8, 10 and 11, in whom this procedure was contraindicated by a haemorrhagic tendency. Liver and spleen scans were performed in all patients using ^{99}Tc^{m} with routine anterior, posterior and lateral views. Evidence of oesophageal varices was sought by endoscopy or radiology. None of the patients had clinical lymphadenopathy and diagnostic scalene or other lymph node biopsy was not performed before the laparotomy for splenectomy. Eight of the 13 patients had lymphangiograms, but these were all interpreted as being normal. Diagnostic splenic aspiration was not utilized. At laparotomy for splenectomy several lymph nodes were taken for biopsy purposes from the root of the mesentery and the para-aortic regions.

Findings after splenectomy

The results of diagnostic splenectomy are shown in *Table I*. There was no immediate operative mortality, although one patient (*Case* 8) died 5 weeks after her operation without leaving hospital.

Patients with positive findings at splenectomy

A definite histological diagnosis was achieved in 6 of the 13 patients. Two patients (*Cases* 2 and 3) who came to medical attention because of pain in the left upper quadrant were shown to have congenital splenic cysts. The diagnosis had been suggested by patchy uptake on the spleen scans. A youngster of 16 (*Case* 6) had been found to have an enlarged spleen at routine school medical examination and splenectomy revealed the diagnosis of Gaucher's disease. No other members of the family were affected and there were no other physical stigmas of the disease. Bone-marrow biopsy and trephine and liver biopsy had been unhelpful. An elderly man (*Case* 10), previously reported (Toghill et al., 1972), was shown to have haemangiosarcoma. Rupture of the spleen precipitated emergency surgery a few hours before splenectomy had been planned. *Case* 1

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ble I: HAEMATOLOGICAL FINDINGS BEFORE SPLENECTOMY AND AT LAST FOLLOW-UP

Case	Sex	Age at splenectomy (yr)	Hb (g/dl)	WBC (× 10⁹/l)	Platelets (× 10⁹/l)	Known duration of splenomegaly before splenectomy	Weight of spleen (g)	Histopathology of excised spleen	Outcome after splenectomy
1	M	28	(a) 12·6	6·0	430	2 wk	1980	Sarcoidosis	Remains well on steroid therapy 3 yr later
			(b) 14·6	6·3	420				
2	M	14	(a) 14·9	6·5	250	1 yr	1310	Splenic cyst	Discharged
3	F	27	(a) 14·5	11·0	280	2 yr	1290	Splenic cyst	Discharged
4	F	66	(a) 10·8	4·4	125	4 mth	2690	Non-specific, (?) idiopathic, non-tropical splenomegaly	Remains well 2 yr later
			(b) 13·6	10·8	391				
5	M	60	(a) 8·3	6·2	120	2 yr	245	Non-specific	Remains in poor health 2½ yr later
			(b) 9·4	10·8	184				
6	F	16	(a) 12·3	5·7	127	14 mth	830	Gaucher's disease	Remains well 2 yr later
			(b) 11·7	17·4	190				
7	M	31	(a) 14·0	7·0	350	8 wk	520	Non-specific	Remains well 3 yr later
			(b) 14·9	7·1	410				
8	F	54	(a) 8·9	10·4	30	2 mth	304	Non-specific	Died 5 weeks after splenectomy with thrombocytopenia
9	M	45	(a) 5·3	1·9	52	3 mth	1570	Non-specific, (?) idiopathic non-tropical splenomegaly	Remains well 8 yr later
			(b) 13·8	7·4	281				
10	M	72	(a) 5·3	5·5	50	2 wk	1125	Haemangio-sarcoma	Died 3 mth later
11	F	73	(a) 8·9	1·5	78	3 mth	660	Non-specific	Well for 21 months after splenectomy. Died from lymphosarcoma 2 yr after splenectomy
12	M	30	(a) 13·8	7·8	250	3 mth	200	Sarcoidosis	Well 18 mth later
			(b) 15·0	14·6	300				
13	M	31	(a) 9·5	1·2	25	2 mth	620	Non-specific	Remains in excellent health 6 mth later
			(b) 14·6	4·9	76				

(a) Findings before splenectomy; (b) findings at last follow-up.

was admitted to hospital as an emergency with a pneumothorax and was found to have an enormously enlarged spleen. Diagnostic splenectomy revealed sarcoidosis, which had seemed unlikely on clinical grounds in view of the massive splenomegaly. *Case* 12, who presented with pruritus, was confidently expected to have a lymphoma, but histological examination of both spleen and abdominal nodes showed sarcoidosis.

Patients with non-specific histology

There were no specific diagnostic features at splenectomy in the other 7 cases. In one patient (*Case* 11), the splenomegaly preceded the development of overt lymphosarcoma by almost 2 years. This patient had been investigated extensively preoperatively for a Coombs negative haemolytic anaemia, leucopenia and thrombocytopenia. Surface counting using ^{51}Cr-labelled erythrocytes showed excess splenic uptake. Splenectomy resulted in a gratifying haematological improvement for 21 months until the patient showed clinical evidence of lymphosarcoma which caused her death 3 months later.

Two patients (*Cases* 4 and 9) had massive spleens that were associated with some features of hypersplenism. Neither of these patients had evidence of excessive splenic uptake on surface counting but each had large splenic red cell pools of 13 and 28 per cent of the RCM respectively. In addition, the plasma volume in each case was increased above the normal value of 34–48 ml/kg. Much of the initial haematological improvement after splenectomy in these patients was likely to have been due to the removal of the large SRCP and reduction of the expanded plasma volume. Both patients have now lived for 2 and 8 years respectively in excellent health.

In 4 other patients with mild to moderately enlarged spleens weighing from 245 to 800 g splenectomy failed either to achieve a diagnosis or to improve the health of the patients, although in *Case* 13 there was a satisfactory rise in the platelet count from a worryingly low level of 30 × 10⁹/l to 87 × 10⁹/l. *Case* 8 had been investigated extensively preoperatively for mild splenomegaly, a normochromic anaemia and thrombocytopenia. This patient died 5 weeks after splenectomy from continuing thrombocytopenia and subsequent autopsy failed to reveal a specific disease process. *Cases* 5 and 7 have now been followed up for 2½ and 3 years respectively and neither has developed any new or diagnostic features.

Table II: RESULTS OF HAEMATOLOGICAL INVESTIGATIONS

Case	RCM (ml/kg)	SRCP (% of RCM)	RCS (T_{50} ^{51}Cr)	Surface counting studies	PV (ml/kg)
3	24·0	0	24 d	No excess splenic uptake	38
4	26·5	13	22 d	No excess splenic uptake	50
7	19·7	18	18 d	No excess splenic uptake	NE
8	16·2	5·5	14·5 d	No excess splenic uptake	NE
9	13·8	28	22 d	No excess splenic uptake	60
11	23·7	6	10 d	Excess splenic uptake (splenic index + 250)	NE

RCM, Red cell mass (normal 25–36 ml/kg); SRCP, splenic red cell pool; RCS, red cell survival (normal 24–28 d); PV, plasma volume (normal 34–48 ml/kg); NE, not estimated.

Table III: DIAGNOSTIC VALUE OF SPLENECTOMY IN SOME REPRESENTATIVE WORLD SERIES

Period	No. of cases	Type of material	No. in whom diagnosis uncertain at splenectomy	Diagnostic splenectomies (%)
(*a*) 1956–66	582	All splenectomies	52	9
(*b*) 1963–68	41	Haematological disorders	0	0
(*c*) 1947–70	200	Haematological disorders	6	3
(*d*) Not stated	104	Haematological disorders	4	4
(*e*) 1961–72	406	All splenectomies	12	3
(*f*) 1944–70	53	Haematological disorders	0	0
(*g*) 1967–71	80	Haematological disorders	10	12·5
(*h*) 1968–76	116	All splenectomies	13	11

Series and origin: (*a*) Herman et al. (1968), USA. (*b*) Christensen et al. (1970), Denmark. (*c*) Schwartz et al. (1970), USA. (*d*) Nightingale et al. (1971), UK. (*e*) McKinnon et al. (1973), New Zealand. (*f*) Ogawa et al. (1974), Japan. (*g*) Ikkala et al. (1974), Finland. (*h*) Present series (1978), UK.

Discussion

Many of the larger series of splenectomies reported in the past 10 years have included a proportion of patients in whom the diagnosis was uncertain at the time of splenectomy. *Table III* includes some representative series from various parts of the world, indicating that up to 12·5 per cent of patients who undergo splenectomy are undiagnosed at the time of operation. In the largest group, Herman and his colleagues (1968) considered that 52 of their 582 patients had had splenectomies primarily for diagnostic purposes. With the more liberal use of liver biopsy, lymphangiography and organ scanning by ultrasound or computerized axial tomography, however, it is likely that fewer cases in the future will need to proceed to splenectomy for diagnosis.

Many authors have pointed to the value of splenectomy in the initial diagnosis of lymphoma (Hyatt et al., 1970; Schwartz et al., 1970; Skarin et al., 1971; Long and Aisenberg, 1974; Case Records of the Massachusetts General Hospital, 1976). Herman and colleagues (1968) found 31 per cent of their cases of diagnostic splenectomy to have lymphoma. However, the wide spectrum of diseases that may be delineated by diagnostic splenectomy includes sarcoidosis (Herman et al., 1968), splenic cysts and abscesses (Herman et al., 1968; Chulay and Lankerani, 1976), primary tumours of the spleen (DasGupta et al., 1965), splenic angioma (Rhochmis, 1970) and splenoma (Bhagwat et al., 1975).

In our 5 patients in whom an accurate histological diagnosis was achieved it was gratifying to be able to assure *Cases* 2 and 3 that they had benign disorders. Previously both had undergone extensive investigation and they had been given a guarded prognosis. It was thought that *Cases* 1 and 6 might be suffering [illegible] lymphoma, though splenectomy showed sarcoidosis and Gaucher's disease respectively, diseases with a somewhat better prognosis. Nevertheless, it must be remembered that splenectomy in Gaucher's disease, though proving the diagnosis, may possibly result in an extension of the osseous and hepatic lesions (Matoth and Fried, 1965) and may also render the child vulnerable to the fulminating infections known to occur in the asplenic state (Ramsay and Bouskill, 1973).

Our own series is characterized by the high proportion of cases (7 out of 13) in which the splenic histology was non-specific, though we realize that some of these cases may eventually proceed to frank lymphoma, as did *Case* 11. Undoubtedly enlargement of the spleen may be a foreboding of subsequent lymphoma, and information derived from diagnostic laparotomy and staging splenectomy in Hodgkin's disease indicates that considerably enlarged spleens may be free from disease (Glatstein et al., 1970; Ell et al., 1975). We believe that two of the patients (*Cases* 4 and 9) are probably examples of the syndrome previously described as idiopathic, non-tropical splenomegaly (Dacie et al., 1969) or primary splenic hyperplasia (Weinstein, 1964). In these syndromes, the spleen may be grossly enlarged without there being consistent or significant histological changes. Splenectomy produces a clinical and haematological improvement without serious disease necessarily developing. Both *Cases* 4 and 9 derived relief from the removal of large uncomfortable spleens, and from the effects of the 'big spleen' syndrome, including pooling of erythrocytes and platelets in the spleen and expansion of the plasma volume. Splenectomy failed to establish a diagnosis in the 4 other patients (*Cases* 5, 7, 8 and 13), and as these patients had only mildly enlarged spleens; there were no other benefits. Certainly their spleens were significantly enlarged (DeLand, 1970; Myers and Segal, 1974) and, in association with obvious haematological abnormalities, there was some basis for diagnostic splenectomy.

Our conclusions are that in some cases splenectomy for unexplained splenomegaly may be a useful diagnostic procedure. When splenomegaly is only mild and there is no evidence of disease elsewhere, the indications for diagnostic splenectomy are arguable. Routine examinations of college freshmen have shown 1 per cent with palpable spleens for which no sinister cause was found after a 6-year follow-up (McIntyre and Ebaugh, 1967). There have also been suggestions that splenic infarction might be responsible for some cases of mild to moderate splenomegaly in otherwise healthy folk, and although results of angiography and scanning may be abnormal, the gross changes may be non-specific (Russell et al., 1976). With the larger spleens the diagnostic yield after splenectomy is likely to be greater, but it must be admitted that even with modern techniques some of the large spleens will be undiagnosed after splenectomy. Nevertheless, in patients with the 'big spleen' syndrome, other benefits may accrue simply from the removal of the very large organ.

Acknowledgements

We thank Trent Regional Health Authority and the Dunhill Research Trust for financial support.

[illegible] DATTA D. V., MITRA S. et al. (1975) Splenoma [illegible] portal hypertension. *Br. Med. J.* **3**, 520.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL (1976) *N. Engl. J. Med.* **295**, 828–834.

CHRISTENSEN B. E., HANSEN L. K., KRISTENSEN J. K. et al. (1970) Splenectomy in haematology. *Scand. J. Haematol.* **7**, 247–260.

CHULAY J. D. and LANKERANI M. R. (1976) Splenic abscess. *Am. J. Med.* **61**, 503–511.

DACIE J. V., BRAIN M. C., HARRISON C. V. et al. (1969) Non-tropical idiopathic splenomegaly (primary hypersplenism): a review of ten cases and their relationship to malignant lymphoma. *Br. J. Haematol.* **17**, 317–333.

DASGUPTA T., COOMBES B. and BRASFIELD R. D. (1965) Primary malignant neoplasms of the spleen. *Surg. Gynecol. Obstet.* **120**, 947–960.

DELAND F. H. (1970) Normal spleen size. *Radiology* **97**, 589–592.

ELL P. J., BRITTON K. E., FARRER-BROWN G. et al. (1975) An assessment of the value of spleen scanning in the staging of Hodgkin's disease. *Br. J. Radiol.* **48**, 590–593.

GLATSTEIN E., TRUEBLOOD H. W., ENRIGHT L. P. et al. (1970) Surgical staging of abdominal involvement in unselected patients with Hodgkin's disease. *Radiology* **97**, 425–432.

HERMAN R. E., DEHAVEN K. E. and HAWK W. A. (1968) Splenectomy for the diagnosis of splenomegaly. *Ann. Surg.* **168**, 896–900.

HICKLING R. A. (1964) Giant follicle lymphoma of the spleen: a condition closely related to lymphatic leukaemia but apparently curable by splenectomy. *Br. Med. J.* **2**, 787–790.

HYATT D. F., SKARIN A. T., MOLONEY W. C. et al. (1970) Splenectomy for lymphosarcoma. *Surg. Gynecol. Obstet.* **131**, 928–932.

IKKALA E., KIVILAAKSO E. and HASTBACKA J. (1974) Splenectomy in blood diseases. *Ann. Clin. Res.* **6**, 290–299.

JANDL J. H., GREENBERG M. S., YONEMOTO R. H. et al. (1956) The clinical determination of sites of red cell sequestration in haemolytic anaemias. *J. Clin. Invest.* **35**, 842–867.

LONG J. C. and AISENBERG A. C. (1974) Malignant lymphoma diagnosed by splenectomy and idiopathic splenomegaly. *Cancer* **33**, 1054–1061.

MCINTYRE O. R. and EBAUGH F. R. (1967) Palpable spleens in college freshmen. *Ann. Intern. Med.* **66**, 301–306.

MCKINNON W. M. P., SANDERS H. S., ZAMORA L. F. et al. (1973) Splenectomy: indications, results and complications in 406 patients. *Ann. Surg.* **39**, 72–74.

MATHOTH Y. and FRIED K. (1965) Chronic Gaucher's disease: clinical observations on 34 patients. *Israel J. Med. Sci.* **1**, 521–530.

MYERS J. and SEGAL R. J. (1974) Weight of the spleen. I. Range of normal in a non-hospital population. *Arch. Pathol.* **98**, 33–35.

NIGHTINGALE D., PRANKERD T. A. J., RICHARDS J. D. M. et al. (1971) Splenectomy in anaemia. *Q. J. Med.* **41**, 261–267.

OGA[illegible] Y., KOBAYSHI M., SAKU M. et al. (1974) *Jap. J. Surg.* **4**, [illegible]-28.

PARKER A. C., MACPHERSON A. I. S. and RICHMOND J. (1977) Value of radiochromium investigation in auto-immune haemolytic anaemia. *Br. Med. J.* **2**, 208–209.

RAMSAY L. F. and BOUSKILL K. C. (1973) Fatal pneumococcal meningitis in adults following splenectomy: two case reports and a review of the literature. *J. R. Nav. Med. Serv.* **59**, 102–114.

RHOCHMIS P. G. (1970) Splenic angioma with thrombocytopenia. *NY State J. Med.* **70**, 2133–2136.

RUSSELL C. D., JONES A. E., JOHNSTON G. S. and HERDT J. R. L. (1976) Arteriographically confirmed focal defect in colloid spleen scan with no gross pathologic lesions; case report. *J. Nucl. Med.* **15**, 376–377.

SCHWARTZ S. I., BERNARD R. P., ADAMS J. T. and BAUMAN A. W. (1970) Splenectomy for haematologic disorders. *Arch. Surg.* **101**, 338–347.

SKARIN A. T., DAVEY F. R. and MOLONEY W. C. (1971) Lymphosarcoma of the spleen. *Arch. Intern. Med.* **127**, 259–265.

TOGHILL P. J. and GREEN S. (1975) Haematological changes in active chronic hepatitis with reference to the role of the spleen. *J. Clin. Pathol.* **28**, 8–11.

TOGHILL P. J., RIGBY C. C. and HALL G. F. M. (1972) Haemangiosarcoma of the spleen. *Br. J. Surg.* **59**, 406–408.

WEINSTEIN V. F. (1964) Haemodilution anaemia associated with simple splenic hyperplasia. *Lancet* **2**, 218–223.

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Erratum

The publishers regret that in the November 1978 issue of the *British Journal of Surgery*, in the article by George A. Khoury et al., 'Tuberculosis of the peritoneal cavity', on pp. 808 and 809 *Figs.* 1 and 3 were transposed.

It has also been brought to our attention that the article by L. E. Hughes and J. F. Forbes 'Early breast cancer', *Fig.* 2 on p. 760 is incorrectly labelled: *c* should read *a* and vice versa. Also, on p. 768 the reference to *Table III* should read *Table II*.

Br. J. Surg. Vol. [illegible] (1979) 66

A hazard of the Eder–Puestow system for oesophageal dilatation

JOHN BANCEWICZ*

THE introduction of the Eder–Puestow system (Puestow, 1955) for oesophageal dilatation, in conjunction with fibreoptic instruments, has been a significant advance (Price et al., 1974). By this technique the stricture is visualized with a flexible fibreoptic oesophagoscope and a guide wire is passed through the stricture via the biopsy channel of the instrument. The oesophagoscope is then withdrawn and dilatation is achieved by passing graded metal bougies over the wire. These bougies have a flexible guide spring at the tip and the shaft is also flexible. The use of entirely flexible instruments probably reduces the risk of oesophageal perforation. In addition, dilatation can frequently be carried out under topical anaesthesia and diazepam sedation. As this system is relatively new, however, it is too early to say whether it is associated with any particular complications of its own. This report describes a complication that occurred during the use of Eder–Puestow dilators and which has not been reported before.

Case report

A 35-year-old woman underwent bouginage of a fibrous stricture in the upper third of the oesophagus which developed after oesophageal resection for carcinoma. This was carried out under general anaesthesia at the patient's request. When one of the larger bougies was withdrawn it was seen that the flexible guide spring had broken off the end of the bougie. This spring is prevented from slipping off the end of the guide wire by an expanded 'fingertip' on the guide wire which guards against oesophageal perforation. An attempt was therefore made to withdraw the spring by simply pulling out the guide wire. Unfortunately this could not be done as the spring appeared to stick at the site of the oesophageal stricture. It was necessary to pass a small, rigid oesophagoscope over the guide wire down to, and almost through, the stricture. Once this had been done, the guide wire and guide spring were removed quite easily.

The reason the guide wire could not be withdrawn is clear from *Fig*. 1. As can be seen, the guide spring had broken off the metal ferrule which is screwed into the rest of the bougie. A sharp spike of spring remained and had become stuck in the stricture. This might have caused marked damage had any force been used to withdraw the guide wire.

It is the author's belief that this untoward event has not been reported before. Our dilators have now been in use for about 2½ years and, as can be seen from *Fig*. 2, the guide spring tends to become distorted with time. This probably results from repeated screwing and unscrewing of the spring and the coils on the metal ferrule become stretched. Users of the bougie system should be aware of this and guide springs that become distorted in this manner should be discarded before breakage occurs. It is planned to include an appropriate warning in the instructions for the use of the bougies (Messrs KeyMed, personal communication).

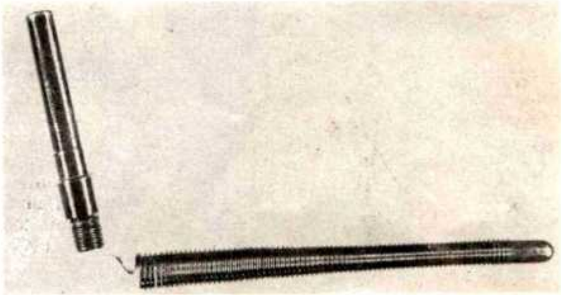

Fig. 1. The broken guide spring.

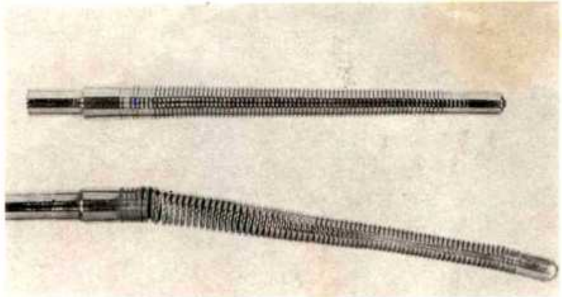

Fig. 2. New and used guide springs, showing the distortion that can occur with time.

References

PRICE J. D., STANCIU C. and BENNETT J. R. (1974) A safer method of dilating oesophageal strictures. *Lancet* **1**, 1141–1142.

PUESTOW K. L. (1955) Conservative treatment of stenosing diseases of the oesophagus. *Postgrad. Med.* **18**, 6–14.

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respondence

Trasylol in primary acute pancreatitis

Sir,

It is always difficult to draw direct comparisons between laboratory and clinical studies. The tests of antitryptic activity of Trasylol in the dog described by Dr Miller (*Br. J. Surg.* **65**, 887) do not bear great resemblance to canine models of experimental acute pancreatitis as the large doses of trypsin used, even in the fourth group of dogs given supplementary Trasylol 10 min later, resulted in death in less than 50 min. Even the more severe forms of canine experimental pancreatitis without Trasylol therapy usually require from 6 to 24 h to result in the death of the animal. Nevertheless, the results presented of the interactions of intravenous trypsin and intravenous Trasylol are in broad agreement with earlier studies (Grozinger, 1966) that the larger the dose of Trasylol and the smaller the time interval from insult, the more effective the drug's antiproteolytic activity.

With respect to the tests of the duration of existence of Trasylol in the blood, Dr Miller found only limited inhibition of trypsin using BAPA as a substrate. These results must be viewed in the light of our knowledge that even when trypsin is complexed with alpha-macroglobulin or alpha$_1$-antitrypsin these complexes still retain trypsin-like activity in terms of splitting this substrate (Ohlsson, 1971; Ohlsson and Tegner, 1973). It is, therefore, possible that complexes of Trasylol and trypsin also retain trypsin-like activity and an ability to split BAPA. Our own laboratory work, which will be published in detail shortly, has shown that very high dosage intravenous Trasylol therapy (20 000 KIU/kg) in the dog is totally effective in preventing death administered up to 6 h after induction of acute pancreatitis (Imrie and Mackenzie, 1977). In terms of clinical acute pancreatitis, both our study (Imrie et al., 1978) and that of the Medical Research Council (MRC Multicentre Trial, 1977) have demonstrated that there is no value in giving a starter dose of 500 000 KIU of Trasylol intravenously followed by a further 4–5 million units over the next 5 days to patients with acute pancreatitis. We are presently assessing in the clinical context a much higher dose of intravenous Trasylol given for a much shorter time, but in the present state of knowledge, Trasylol should be withheld in the treatment of primary acute pancreatitis.

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GROZINGER K. H. (1966) Pancreatitis: progress in management. *Surgery* **59**, 319–326.

IMRIE C. W. and MACKENZIE M. (1977) High dosage effective Trasylol therapy in experimental acute pancreatitis. *Br. J. Surg.* **64**, 828.

IMRIE C. W., BENJAMIN I. S., FERGUSON J. C. et al. (1978) A single-centre double-blind trial of Trasylol therapy in primary acute pancreatitis. *Br. J. Surg.* **65**, 337–341.

MRC MULTICENTRE TRIAL (1977) Death from acute pancreatitis. *Lancet* **2**, 632–635.

OHLSSON K. (1971) Experimental pancreatitis in the dog. Appearances of complexes between proteases and trypsin inhibitors in ascitic fluid, lymph and plasma. *Scand. J. Gastroenterol.* **6**, 645–652.

OHLSSON K. and TEGNER H. (1973) Experimental pancreatitis in the dog. Demonstration of trypsin in ascitic fluid, lymph and plasma. *Scand. J. Gastroenterol.* **8**, 129–133.

Book reviews

Achalasia of the Cardia

H. R. S. Harley. 215 × 135 mm. Pp. 174, with 83 illustrations. 1978. Bristol: Wright. £10·00.

THIS monograph on a not particularly common condition can be divided into two parts. The first three chapters are concerned with theoretical considerations and the latter part of the book goes into the clinical manifestation. The theoretical considerations are divided into morbid anatomy and histology, motility and aetiology. Much of the morbid anatomy is not yet fully understood and it is doubtful if it is necessary to carry out motility studies to establish the diagnosis of achalasia. Little is known for sure about the aetiology. Added to all this the text of these sections is so interspersed with references, or perhaps the references in places are interspersed with text, as to be almost unreadable. If there is to be another edition, then it is suggested that another system of references should be adopted.

When the author comes to describe the clinical aspects he is clearly much more at home and he gives a lucid account of the symptomatology based on his own experience and he very properly stresses the frequency of pain as a symptom of a condition usually thought to cause only dysphagia. As far as treatment is concerned the author is a strong advocate of a transthoracic Heller's operation and there is an interesting discussion on the optimum extent of the incision in the oesophageal muscles.

It is a pity that the many X-ray illustrations are poorly reproduced and so small, but this, presumably, is in the interests of economy.

J. W. P. GUMMER

The Care of Congenital Hand Anomalies

Adrian E. Flatt. 245 × 168 mm. Pp. 371 + viii, with 745 illustrations. 1977. St Louis: Mosby. £27·20.

THIS book is, as the author says, 'a personal report to describe one man's surgical approach and philosophy in care and dealing with these problems'. This is a good start because so often nowadays a book of this sort relies for its content upon numerous authors who, in spite of careful editing, inevitably overlap and whose style of writing inevitably differs.

The role of reconstructive surgery in congenital hand deformities is carefully considered having due regard for the parents and relatives and indeed for the child. It is not often that surgery can make a hand look normal, but quite frequently the functional capacity can be increased considerably. In childhood, as the author points out, congenital deformities are far more of an embarrassment to the parents than to the patient and the surgeon has to be very wary lest he fall into the trap of treating the parents rather than the child.

This is a very down to earth account of the commoner deformities that can affect the hand and fingers and the ways in which the disabilities can be ameliorated. The diagrams and illustrations are superb and are carefully chosen to illustrate and enlarge the text. There is a very comprehensive bibliography and an equally useful glossary. The whole work is rounded off by a unique 'syndromes' index.

I found this a delightful book and Adrian Flatt's easy style of writing is a pleasure to read. The production is excellent and selling in this country at £27·20 this is good value.

DONAL BROOKS

Instructional Course Lectures: The American Acad Orthopaedic Surgeons.

Chairman: H. A. W ssinger. 278×214 mm. Pp 227 with 236 illustrations. 1977. St Louis: Mosby. £22·00.

The intention of this book as stated in the brief preface is to select subjects which are important to the orthopaedic sur yet might not appear elsewhere in more conventional litera-ture. This aim is certainly achieved and most of the chapters deal with their subject in a comprehensive manner.

The first section on orthopaedic sepsis reviews both infec-tions of bone and joint and presents attitudes towards h prevention of surgical sepsis, the latter being a subject discussed in recent years. However, it was in th section on hand surgery that I found the greatest Excellent comprehensive chapters on the subjects of plexus lesions, skin coverage the injured h struction of the spastic upper to read and of equal value as paedic specialists as they are ist ing. In section three th subjec is discussed in an equ y int

The *Instructional Cours Le* excellent reading. These are bc ters rather than to read through. available in the library of every instit surgeons are training or practising. Ev do not wish to purchase this boo almost certainly wish to have access to it

ID PATON

Diseases of the Gall Bladder and Biliary System

Edited Leslie J. Schoenfield. 253×175 mm. Pp. 362+xiii. 1977. Chichester: Wiley. £21·75.

This is a well-written text, but it is probably for library consulta-tion rather than personal ownership. The most important contribution is on the topic of gallstones with an excellent discussion of the current status of medical treatment which, quite appropriately, occupies about half the text. The remainder of the book is an up-to-date review of our current knowledge of the less common disorders of the biliary tract. The figures and tables are well selected, and the radiograph reproductions of good quality.

There have been so many books on this and related topics in the past few years that it is difficult to assess this monograph in perspective. For a surgeon who professes a special interest in biliary problems, this is a very appropriate reference. It is engagingly written in a personal way which makes it easy to read and it contains most of the important references.

C. G. CLARK

Butterworths' Medical Dictionary

Edited Macdonald Critchley. Second edition. 285×225 mm. Pp. 1942. 1978. London: Butterworths. £45·00.

Beginning in fine form with a preface that alludes to such varied literary giants as Dr Johnson, Dylan Thomas, Sir William Gowers and Voltaire, the editor straightway warns us that he is one who still embraces archaicisms, not because they still might be needed, like old junk in a spare room cupboard, but from the fact that life is, from time to time, breathed into the dead bones of such memorabilia during their routing out by students of today, as long as they have the means to understand what they find. As one who remembers an instance of much distress and a near fatality that followed upon the use of the word 'singultus' in a crucial context in GP's letter instead of the more widely understood 'hiccup', feel that there are two ways of looking at such latter day sil-hunting. Yet it is right that we should be reminded Philistines we doctors are when it comes to the writing air prose. We really cannot hear too often the wise advice Richard Asher, Charles Thorne or Hugh Dudley, yet ost of us go on writing gobbledygook, quite unaware of remedial advice that is close to hand for anyone who eps Fowler on his study shelf.

How about eponym ably and very properly, keeps them in concern for the origins of medical knowledg shown in the elegant use of proper names that wise be forgotten, even though in the Unite example, Crohn's disease has become regional an imperfect description and nowhere near a same can be said when thromboangiitis obl a s trasted with the far more acceptable Buerger's disease.

The name w contributors form a most exclu e list are many of the ot just experts, though they numental volume. It includes f all known fistulas (with correct mammary from another that is id impartial entry on the National ation Act (1973) and a dozen closely aments of man. What a help such a who needs accurate and reliable guidance ing himself to unforgiving print.

cism, on a matter that no doubt was decided m the outset, concerns the almost total lack of detail in the numerous entries under the names of distinction and importance, or the lesser person who would be useful to know something more than the year of their birth, their work and where they lived. Still, their contributions are listed, defined, and I suspect, complete.

The new *Butterworths' Medical Dictionary* is a must for our libraries, and most medical writers would be helped by owning one. At £45, by the values of today, it is cheap at the price and at the same time a treasure to possess.

H. H. G. EASTCOTT

Current Practice in Orthopaedic Surgery

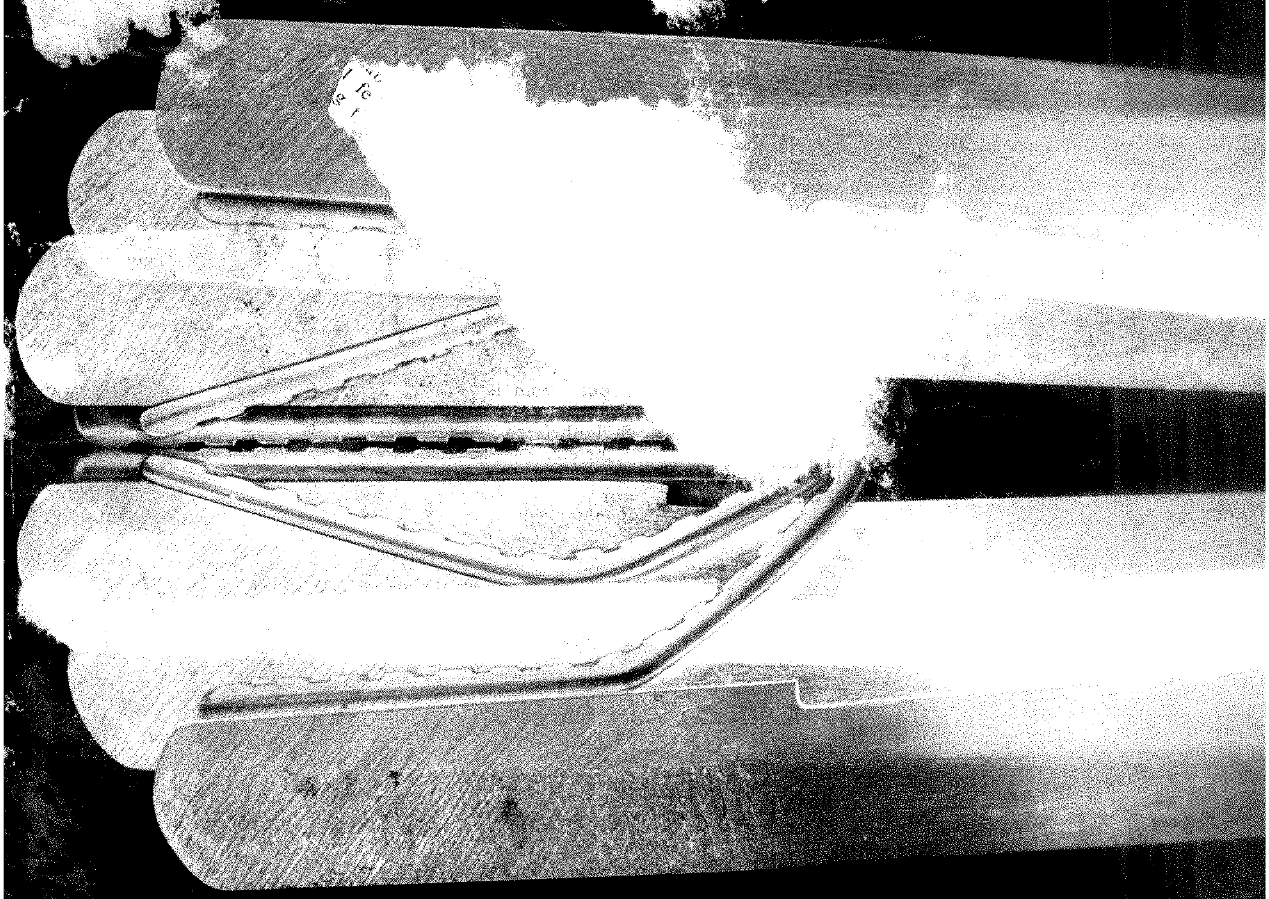
Edited Ahstrom. 246×170 mm. Pp. 271+vii, with 282 illustra-tions. 1977. St Louis: Mosby. £24·80

A collection of isolated topics, each by a different author is bound to be uneven, but the general standard of this book is high and some of the chapters are outstanding. The book opens in fine style with an excellent review of surgery of the rheumatoid hand, marred only by the occasional absence of clear guidance on the selection of procedures. The chapter on scoliosis in adults, without saying anything new, contains much that may be unfamiliar but helpful to the less specia-lized orthopaedic surgeon dealing with back problems. The account of replantation of amputated limbs utilizing micro-surgery is splendidly practical and commendably brief; its guidelines should avert some foolhardy operations in this field. In the chapter on the rheumatoid knee there is a wel-come realization of the importance of correlating the type of prosthesis with the extent of joint damage. However, although the overall account is informative and well worth reading, the follow-up is too short and the case summary on p. 181 is so dreadfully printed that it should be used as an example of how not to do it.

Sports medicine of the neck and back is discussed in a manner which is probably appropriate to practice in the United States, but would find little application in Great Britain. The account of the problem back contains some use-ful clinical tips and has an admirable emphasis on psycho-logical aspects. The treatment of hip fractures is faithfully catalogued, detailing the problem, the difficulties and the suggested answer. The now almost statutory review of embolic problems is adequate rather than sensational, but the combi-nation of social compassion and cost-effectiveness in the Californian management of severely handicapped children is exciting and could usefully be imitated here.

The binding is elegant, the illustrations clear and the text printed on good quality paper; but £24·80 is much too much for this small book and may well price it out of the British market.

A. GRAHAM APLEY



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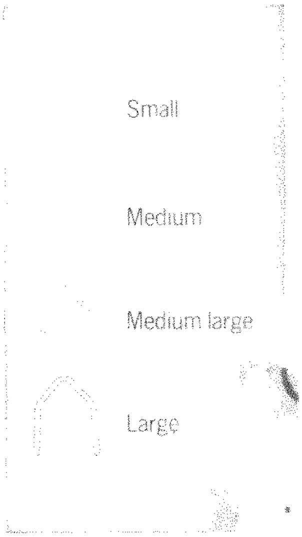

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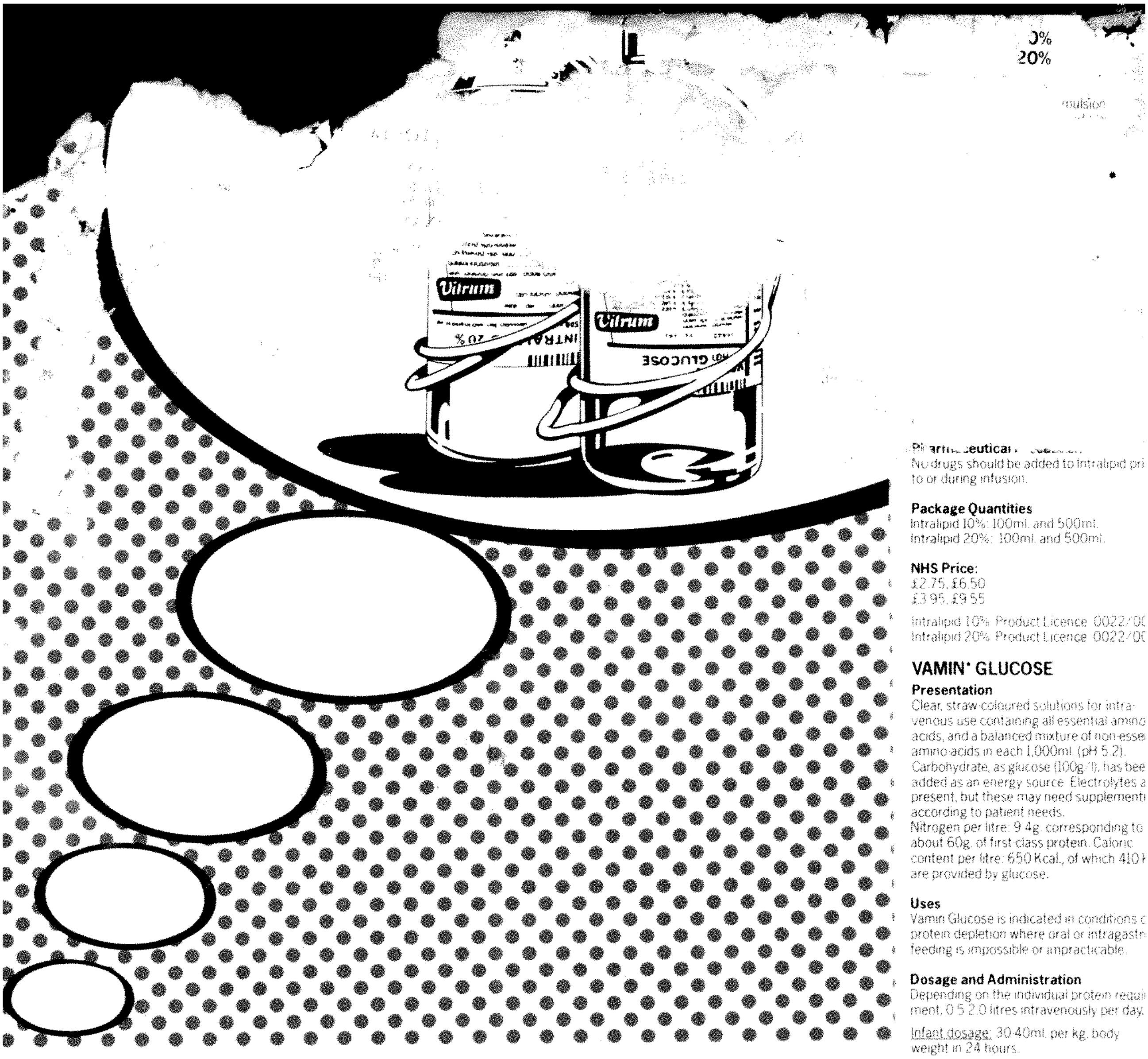

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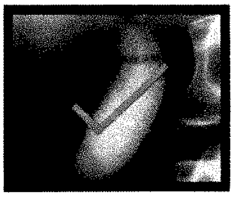

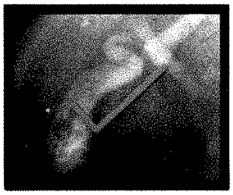

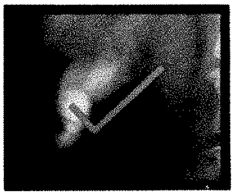

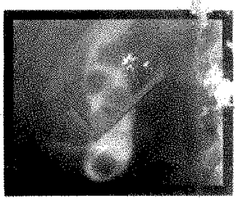

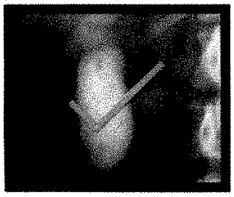

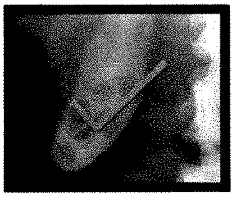

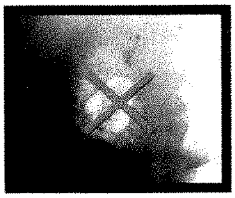

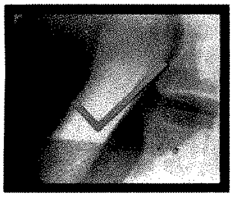

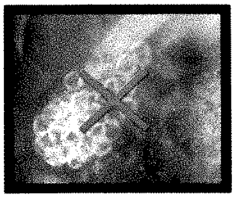

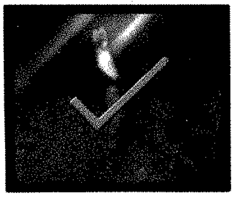

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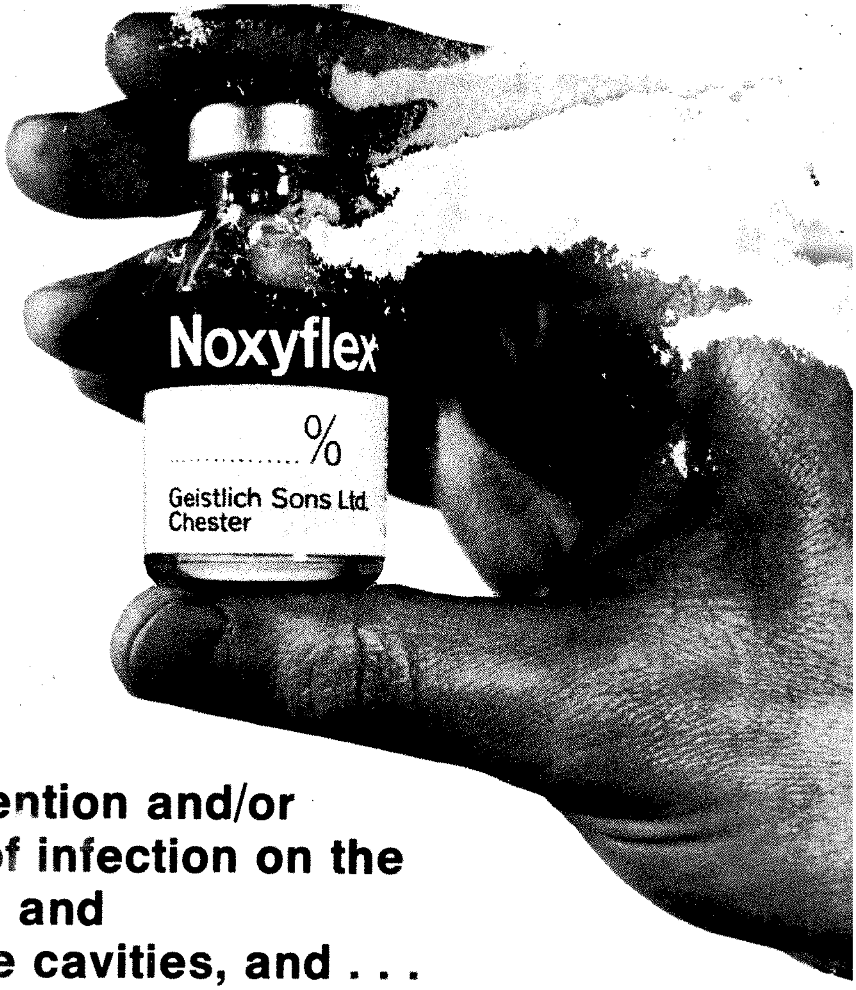
Reference 1 Maton, P. N., Iser, J. H., Murphy, G. M. and Dowling, R. H. (1977) Efficacy of, withdrawal from and resistance to chenodeoxycholic acid treatment in patients with gallstones Gut, *18*, A976 (abstract)

2 Thistle, J. L., Hofmann, A. F., Ott, B. J. and Yu, P. Y. S. (1976) Gallstone dissolution with chenodeoxycholic acid 1969–1976 The Mayo Clinic Studies Gastroenterology 70 943 (abstract)



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REFERENCES
1. Br. J. Surg. (1976), **63,** 978
2. Br. J. Surg. (1978), in press
3. Br. Dent. J. (1977), **143,** 77.

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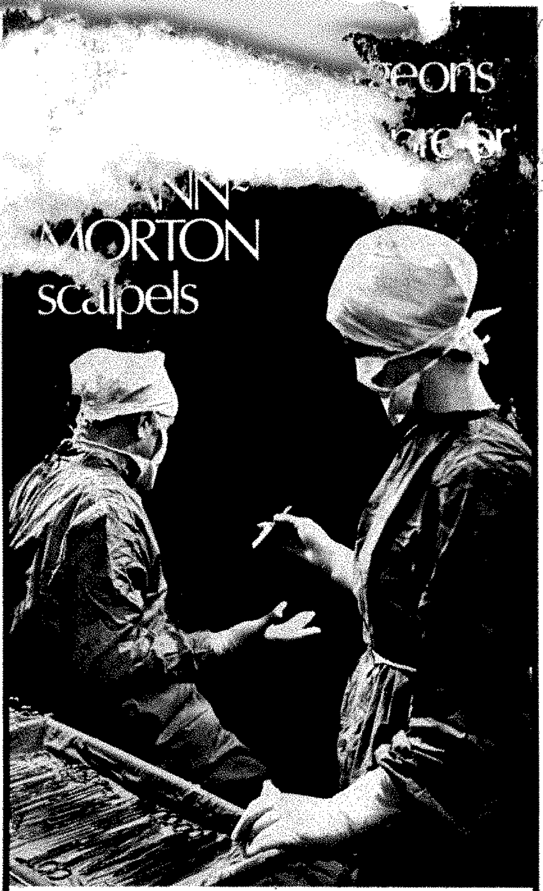

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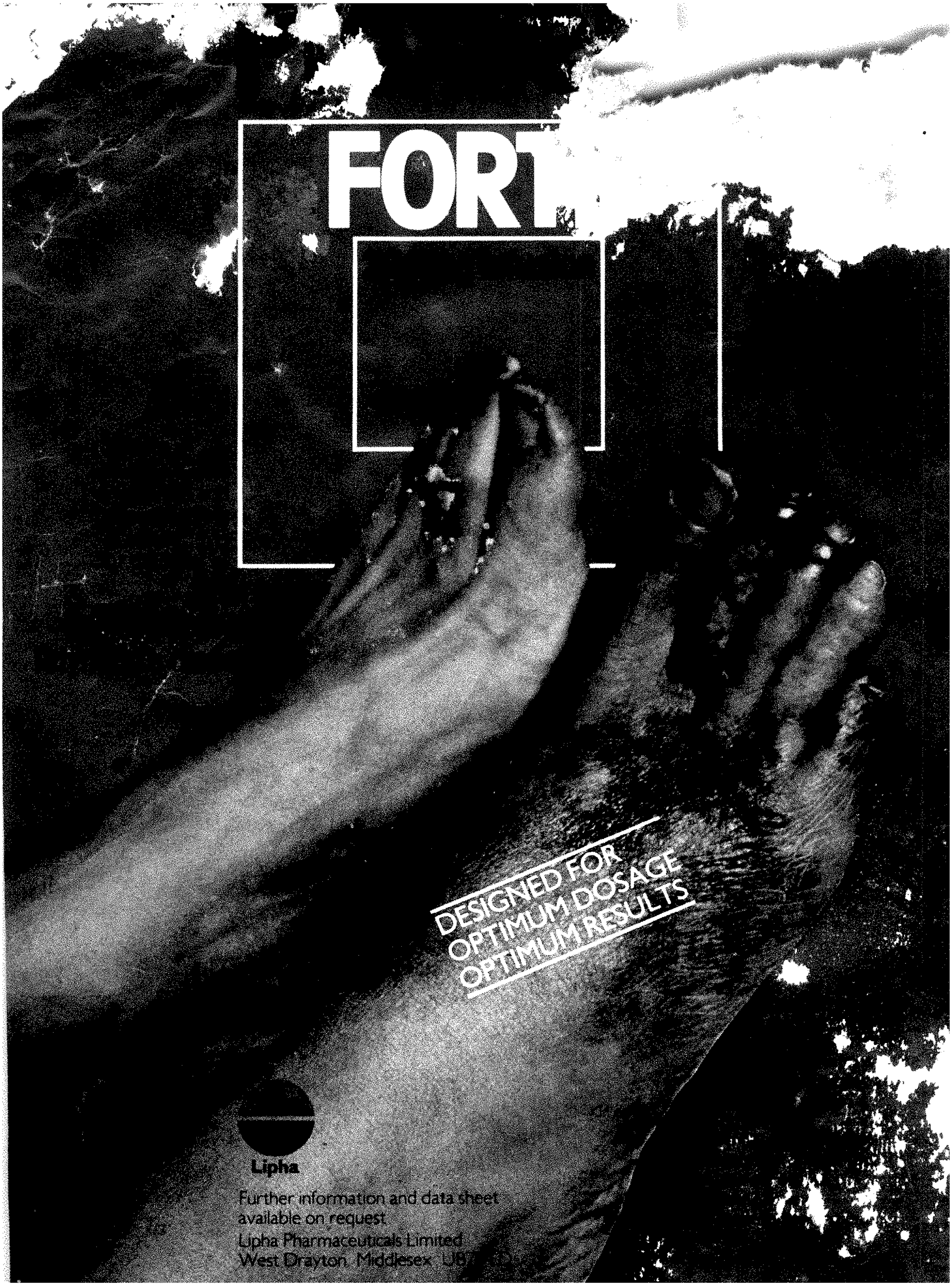

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Br. J. Sur, Vol. 66 (1979) 69–79

Obstructions of the bile duct*

LORD SMITH OF MARLOW†

SIR WILLIAM MACEWEN was not only a towering figure in the surgical history of Britain, he was, from the accounts of all those who knew him, intensely individualistic, a man who inspired contemporaries and successors alike with the desire to copy, to emulate if they could. Sir Gordon Gordon-Taylor, in his Cavendish Lecture of 1958 entitled 'On tradition', pointed out that there are some traditionalists who themselves founded a lasting personal tradition, and as examples he cited Rutherford Morison, Wilfred Trotter, Grey Turner and Macewen. Gordon-Taylor himself was individualistic to a degree and it is to me pleasant, and nostalgic, to recall 'G.-T.' today, for he was not only extremely kind to me when I was a very young surgeon but largely responsible for stimulating in me a particular interest in the surgery of the pancreas, liver and bile ducts. It was G.-T. who said to me in the 1940s, 'If this is the field you're interested in, go to Boston and watch Dick Cattell operate'—good advice, indeed, which I took and consequently saw the most beautiful operating I have ever seen, as well as starting a close friendship which lasted until the untimely death of Dr Cattell at the early age of 62. He, too, was immensely individual in his approach to major surgical problems and in his management of patients. One cannot help wondering what any of these three, Macewen, Gordon-Taylor and Cattell, would have made of the suggestion today that important decisions in surgery should be 'consensus' decisions, taken by a committee rather than by a single surgeon in whom, in any case, final responsibility must remain vested.

All of this leads me to say that I do not think I need apologize, in [illegible] Macewen Lecture upon bile duct obstruction, for starting by saying that this will largely be an account of a personal assault, over a period of rather more than thirty years, upon the problems posed by one single particularly difficult variety of obstruction and that, though I shall refer from time to time to the work of those who have influenced my own thinking, if there be some who have come hoping for a comprehensive survey of everything that has been written upon all varieties of biliary obstruction, they will be disappointed.

Although I obtained my Fellowship and was already engaged in surgical practice before World War II, it was in 1946 that I became a consultant at St George's Hospital, and it is of the 31 years that have followed of which I shall speak. Records going back over a period as long as that are necessarily incomplete, and although I kept from the start personal records of patients in the field of surgery that I had decided interested me most, the figures I am about to quote will be a few short of the actual total number of patients treated.

Between May 1946 and July 1977 I operated upon 3527 patients with biliary obstruction (*Table I*). The fact that this series includes more than twice as many traumatic bile duct strictures as gallstone obstructions does not, of course, mean that strictures are more common than stones in the common bile duct but simply that surgeons are in general happy to refer strictures to a specialized centre, particularly if the patient has already had several unsuccessful operations, whilst they will deal with the gallstone obstructions themselves. It is of bile duct strictures that I shall mainly talk to you today, but first I shall briefly refer to the other causes listed and make a few personal comments about these.

Table I: CAUSES OF BILE DUCT OBSTRUCTION IN 3527 PATIENTS OPERATED UPON BETWEEN MAY 1946 AND OCTOBER 1977

Stone		740
Cancer		862
Pancreas and periampullary	634	
Bile duct	122	
Gallbladder	28	
Metastatic	78	
Pancreatitis and its complications		284
Chronic sclerosing cholangitis		39
Miscellaneous (hydatid; other parasitic; congenital; lymphoma etc.)		48
Traumatic stricture		1554
Operative trauma	1539	
Others	15	
Total		3527

Malignant obstruction

Of the primary cancers, we need spend little time upon carcinoma of the gallbladder invading the porta hepatis and occluding the hepatic duct system. This tumour is almost always highly malignant and even palliation of the jaundice is usually difficult to achieve,

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* The Sir William Macewen Lecture, delivered in Glasgow, November 1977.

† 149 Harley Street, London W1.

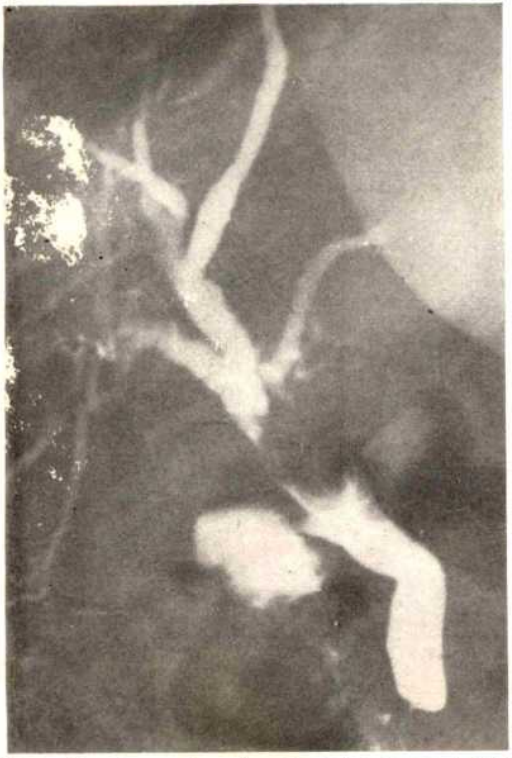

Fig. 1. Percutaneous transhepatic cholangiogram showing a primary carcinoma of the common hepatic duct.

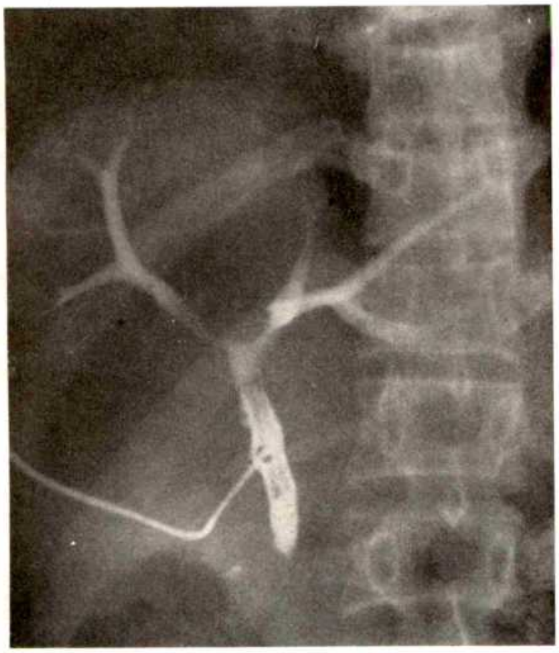

Fig. 2. T tube cholangiogram showing an early carcinoma at the confluence of the hepatic duct system.

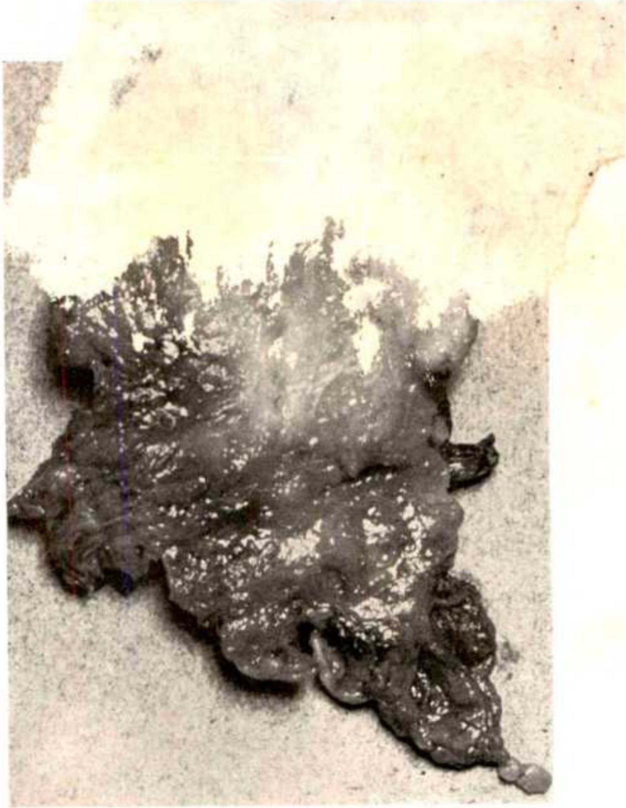

Fig. 3. Resected carcinoma of the confluence of the hepatic duct system.

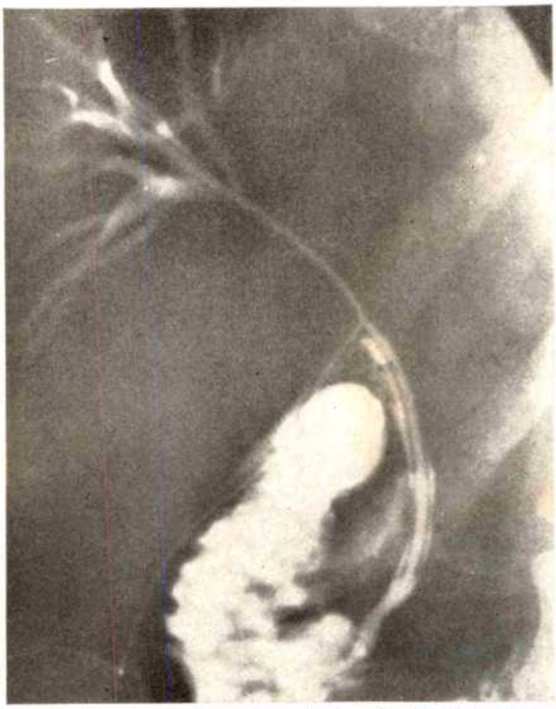

Fig. 4. Dilatation and insertion of a long T-tube through a non-resectable carcinoma of the common hepatic duct. Cholangiogram 1 year later: patient asymptomatic.

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[illegible] th[illegible] [illegible] surgeon ex[illegible] the [illegible] of a [illegible]ced patient and failing to mak[illegible] [illegible]nite diagnosis, or making an incorrect diagnosis of sclerosing cholangitis if a biopsy from tissue adjacent to the tumour is reported as showing merely fibrosis and a few inflammatory cells. The proper use of cholangiography, preoperative and peroperative, from above (transhepatic) and below the lesion by endoscopic retrograde cholangiopancreatography (ERCP) will eliminate most, but not all, of the errors in diagnosis.

A few tumours of this kind are resectable (*Fig*. 3), continuity of the biliary tract being restored by an adaptation of the technique I shall describe shortly in dealing with surgery for benign hilar strictures. For most, however, palliation of the biliary obstruction is all that can be achieved. This may be effected by dilatation of the malignant stricture and the insertion, as a stent, of a T tube or transhepatic tube (*Fig*. 4), including the ingenious U tube operation described by Terblanche and his colleagues (1972); by intrahepatic cholangiojejunostomy (Longmire and Sanford, 1949) (*Fig*. 5), or, occasionally, by intrahepatic cholangiocholecystostomy (*Figs*. 6, 7 and 8) in those

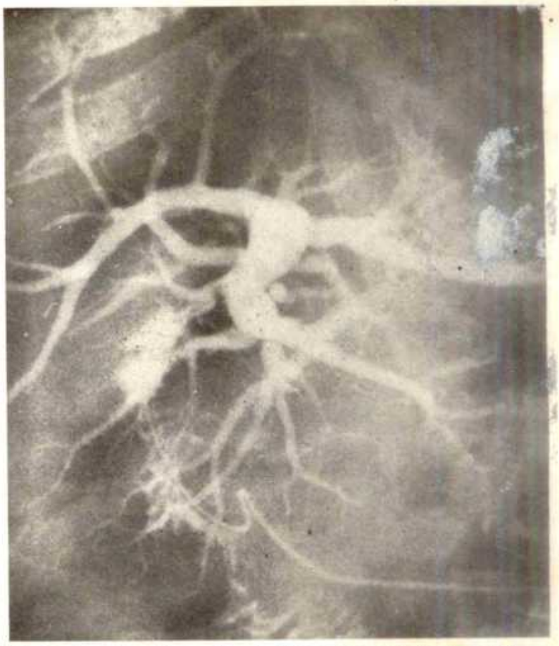
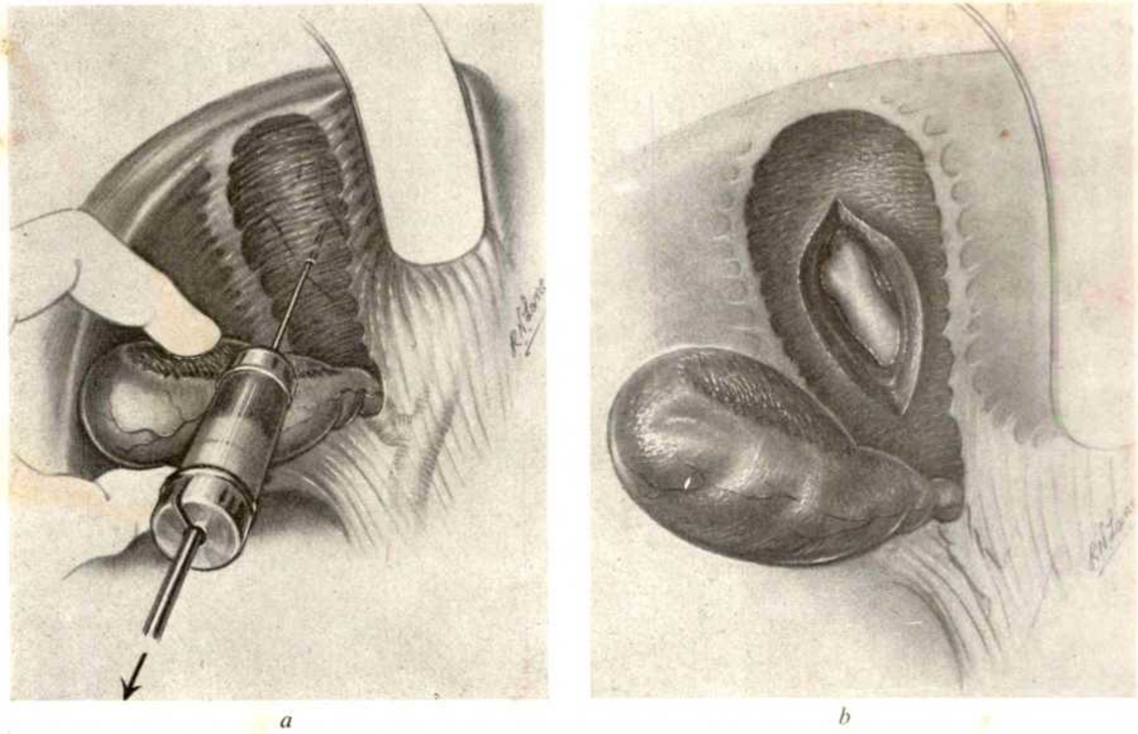


Fig. 5. Intrahepatic cholangiojejunostomy within the right lobe of the liver for non-resectable carcinoma of the common hepatic duct.



a *b*

Fig. 6. Intrahepatic cholangiocholecystostomy; identification and exposure of a dilated intrahepatic duct.

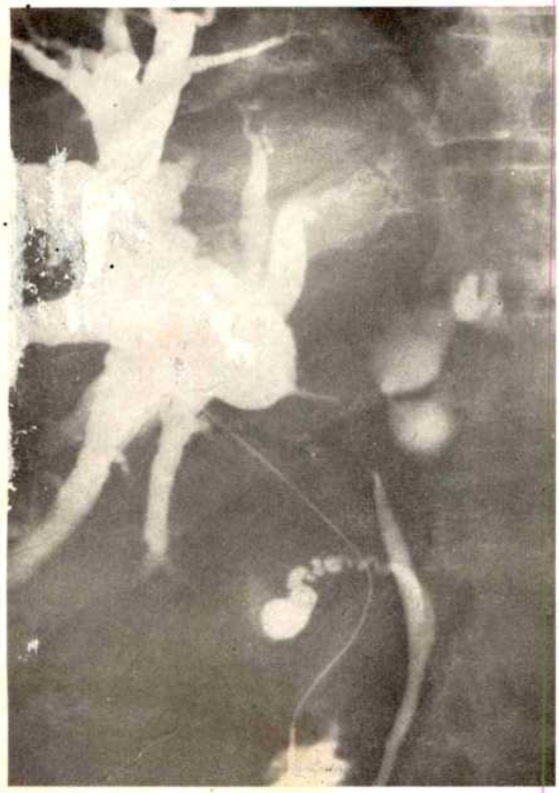


Fig. 7. Carcinoma of the common hepatic duct shown by percutaneous transhepatic cholangiography. Some contrast medium gets past the stricture and part of the gallbladder can be seen. Note the proximity to the dilated intrahepatic ducts, allowing cholangiocholecystostomy.

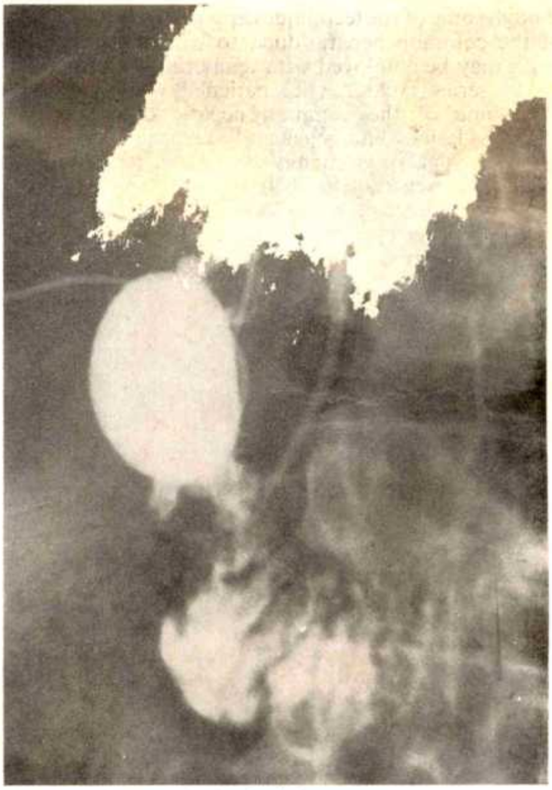


Fig. 8. Intrahepatic cholangiocholecystostomy; a post-operative cholangiogram through an indwelling tube shows contrast medium reaching the duodenum via anastomosis, gallbladder, cystic duct and common bile duct.

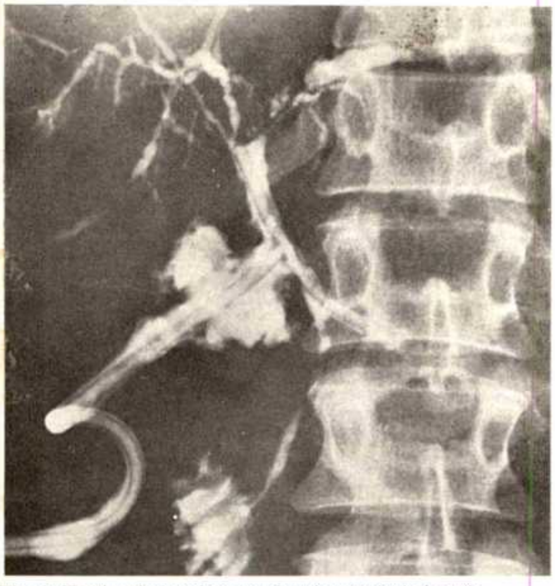


Fig. 9. T tube cholangiogram showing typical chronic sclerosing cholangitis

cases where the gallbladder is normal and the cystic duct joins the common bile duct low down, well away from the tumour. In contradistinction to carcinoma of the gallbladder, primary carcinoma of the common hepatic duct often grows slowly and is slow to disseminate. Resection, if possible, and palliation of the jaundice if not, are therefore well worth while and patients will often live for several years thereafter.

Carcinoma of the hepatic duct system is not infrequently confused with a much rarer condition, chronic sclerosing cholangitis, of which 39 cases are included in my series. Here the strictures are commonly multiple, the intrahepatic and extrahepatic biliary tree being diffusely and widely involved, the cholangiographic appearances being usually quite different from those of a carcinoma (*Fig.* 9). However, there is a variety of diffuse carcinomatosis of the duct system which may produce a diagnostic problem, and radiological differential diagnosis can therefore occasionally be difficult.

Treatment of chronic sclerosing cholangitis is unsatisfactory. Improvement has been observed after treatment both with steroids and with immunosuppressive drugs, but the usual course is unfavourable, leading eventually to an intractable biliary cirrhosis.

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Traumatic strictu

I move on now to my main topic, traumatic stricture of the bile duct. Regrettably in almost all of the 1554 patients with strictures, the cause was damage to the duct during a cholecystectomy, and lest it be thought that these are mostly patients from abroad seeking help in Britain, *Table II* shows the countries in which the first operation had been performed. As can be seen, some three-fifths of the strictures, more than 900 of them, were 'home-grown'.

Every so often there appears in print the suggestion that to damage a bile duct during a cholecystectomy is just bad luck, a natural hazard as it were, and never really the surgeon's fault—in fact, just as likely to happen with an experienced consultant as with an inexperienced junior. This is not borne out by my figures, for, as shown in *Table III*, of 400 unselected cases a consultant was responsible in 62 (15 per cent), whilst in 338 (85 per cent), a junior had been operating on his own.

How does the injury occur? First, technical difficulty and severe inflammatory pathology obscuring the anatomical landmarks are not common causes of this disaster. All too frequently the patient is a thin, young woman, the ducts mobile and normal or small in calibre and the surgeon responsible describes the operation as easy and damage to a duct as beyond his comprehension. The more common causes include an inadequate incision and poor exposure, poor illumination, poor anaesthesia, poor assistance, ignorance of possible anatomical anomalies and a failure to make certain identification of the anatomical structures. Maingot (1977) is right in adding fatigue as a factor, commenting 'It is a mistake to carry out biliary tract surgery towards the end of a long session of operations when the surgeon may be tired or under some tension'. It is also a mistake to insist upon removal of every millimetre of a normal cystic duct.

Diagnosis of trauma to a major duct

Damage to a major bile duct may be recognized during an operation (*Fig.* 10), diagnosed in the immediate postoperative period, or identified at a later date, after the patient has left hospital.

If the operation has been completed without evidence that anything untoward has occurred, the early onset of a deepening obstructive jaundice will naturally arouse suspicions that the common bile duct or common hepatic duct has been accidentally ligated. More commonly, a main extrahepatic bile duct may have been incised, torn, crushed or even divided. In this circumstance, from the day of the operation a profuse discharge of bile will indicate a serious duct injury. In a high proportion of cases of this kind the discharge of bile eventually stops, but optimism on this score is shown to be an illusion as the patient slowly becomes icteric. Sometimes the fistula will reopen with relief of the jaundice and then close again with return of the jaundice. This sequence of events is a not uncommon way for a bile duct injury to present. The picture may be further complicated by subphrenic or subhepatic sepsis as the result of infected bile pooling under the liver or above. Occasionally, the injured duct may turn out to be an anomalous duct, but unfortunately this is only rarely the case.

A relatively minor ductal injury may result in a temporary fistula which eventually dries up completely, leaving a patient who is apparently perfectly well. Later a stricture develops at the site of the injury; the existence of biliary stasis is signalled by the onset first of attacks of cholangitis and later by the slow development of obstructive jaundice. Occasionally, this may occur after the main common hepatic duct has been totally divided and the patient then develops a spontaneous internal fistula into the duodenum. Such a fistula does not result in a spontaneous cure, for,

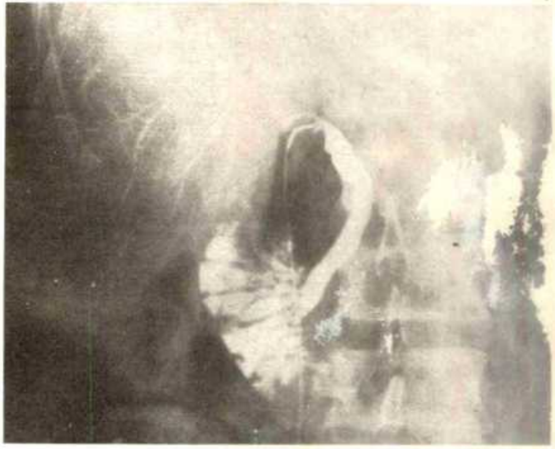


Fig. 10. Peroperative cholangiogram through the cystic duct, clearly showing an injury to the common hepatic duct just above the cystic duct.

Table II: COUNTRY OF ORIGIN OF PATIENTS WITH TRAUMATIC STRICTURES OF THE BILE DUCT (MAY 1946 TO OCTOBER 1977)

Country of origin	No.
United Kingdom	909
North America	26
South America	16
Australia and New Zealand	36
South Africa and Rhodesia	18
India, Pakistan, Sri Lanka	114
South-East Asia	48
Europe	246
Middle East	127
North Africa, Central Africa	14
Total	1554

Table III: THE SURGEON RESPONSIBLE FOR POST-CHOLECYSTECTOMY BILE DUCT STRICTURE*

Operation performed by consultant	58
Operation performed by registrar assisted by consultant	4
Operation performed by registrar with consultant not present	338

* Analysis of 400 patients from the UK selected at random.

being small and not lined with epithelium, the stoma is inadequate from the start and tends to contract with the passage of time. Biliary stasis is further complicated by the development of stones and biliary sludge within the intrahepatic bile ducts; clinically, the patient develops intermittent jaundice and recurrent cholangitis with bouts of high fever, perhaps with rigors.

One further way in which a duct injury may manifest itself should be mentioned. Leakage of bile into the peritoneal cavity does not always produce a severe peritonitis. The evil reputation of biliary peritonitis is probably due to the fact that the leakage is so often of infected bile, leading to a rapidly spreading bacterial peritonitis, rather than merely chemical irritation. Occasionally a cholecystectomy is followed by a slow progressive distension of the abdomen in a patient who remains remarkably well. It is possible for 4–5 litres of bile to collect in a greatly distended abdomen in this way, the patient complaining merely of the increase in abdominal size and pressure and the difficulty of breathing caused by this, a mild icterus developing from the absorption of bile pigment.

Preoperative management
The presence of major injury to a bile duct is usually evident and the necessity for a further operation clear. Preoperative investigations should include a full blood picture, liver function tests, electrolyte estimation and an estimate of renal function. Correction of any deficit brought to light must include administration of vitamin K by intramuscular injection. The patient will often be pyrexial with a high leucocyte count and it is important to decide whether the infection lies within the bile ducts, in other words whether the patient has cholangitis, or whether it is due to a subphrenic abscess which should be drained, leaving the repair of the bile duct injury to a later date. Immediately before operation percutaneous transhepatic cholangiography is useful to outline the dilated bile ducts within the liver and to demonstrate the site of the stricture. This is a more helpful use of radiology than mere demonstration of the duct below the lesion by ERCP.

Operative technique
If it is recognized during the operation that the common bile duct or common hepatic duct has been damaged, immediate repair should be carried out, employing the smallest possible number of the finest sutures necessary to reconstruct the duct. A T tube should be placed in the duct through a separate stab incision, and the majority of surgeons with particular experience in the surgery of the injured duct believe that this T tube should be left in place for a period of at least 3–4 months.

When operating to repair a long-standing stricture of the common hepatic or common bile duct, an ample incision giving good exposure is mandatory. Before approaching the porta hepatis the surgeon should routinely mobilize thoroughly both lobes of the liver and the whole of the right colon so that the latter can be removed completely from the right upper quadrant of the abdomen and packed away downwards and to the left, in order to secure a wide exposure in the area where the ductal damage has occurred.

The antrum, pylorus and duodenum are carefully mobilized away from the liver and retracted downwards. In dissecti[illegible]um from the porta hepatis, a fistula betw[illegible] hepatic duct above the stricture and [illegible] duodenum is quite often present an[illegible] specifically be looked for. If found, it is [illegible] small opening into the duodenum is [illegible]. The dilated common hepatic duct abo[illegible]ure is sought in the dense scar tissue in [illegible]atis, if necessary a needle and syringe being used to identify the duct. Occasionally the injury is at such a high level that there is no common hepatic duct left and in the scar tissue are discovered the ends of the right and left common hepatic ducts, opening independently. The duct or ducts are mobilized as far as possible and dissected free from scar tissue. Using probes and operative cholangiography the anatomy of the duct system above the stricture is displayed and the interior of the duct carefully inspected to determine the level at which the normal epithelial lining is visible. Bile from the intrahepatic ducts is taken for culture; often this is very dirty, containing a great deal of biliary mud and sometimes small stones. It is important before proceeding with the repair to wash out the duct system, and the most effective way of doing this is to insert a catheter that fits tightly into the opened duct and to distend the intrahepatic biliary system by injecting, slowly, up to 60 ml of sterile water or saline. The catheter is then pulled out and as the fluid rushes out from the liver it brings with it solid debris often lying high inside the smaller intrahepatic ducts. This procedure is repeated several times until the fluid returns clear. The operation can now continue.

The anastomosis
The late Dr Cattell in the Lahey Clinic recommended, even in late cases where several unsuccessful attempts had been made at repair, that end-to-end anastomosis of the bile duct should nevertheless still be carried out (Cattell, 1947). Today most surgeons working in this field believe that a better long term result is likely to be obtained with anastomosis of the common hepatic duct to the jejunum and this is the most popular procedure at the present time.

In 30 years of endeavour I have changed my mind more than once in regard to the technique likely to yield the best results and the stages through which my own thoughts have passed [illegible] considered not only possibly of interest bu[illegible]o those anxious to work in this somewhat exciting field.

On the face of it, one m[illegible] imagine that the repair of a divided hollow tu[illegible]ch as a bile duct, would best be effected by end-[illegible] anastomosis, and as a young surgeon immedia[illegible]ter World War II I accepted without much fur[illegible]ought Dr Cattell's assurance that this was, in [illegible] case.

In my early cases, therefo[illegible] upon an end-to-end anastomosis (*Figs.* 1[illegible]), [illegible]nly for a recently divided duct but also in the late case after excision of the resultant stricture. Like Cattell I dissected out the contracted lower end of the duct and, mobilizing the head of the pancreas, shifted this up into the porta hepatis so that, even in the case of a hilar stricture, anastomosis could be performed without tension. Like Cattell, however, I found that far too many patients returned, having initially done well, with a recurrent stricture at the site of the anastomosis (*Fig.* 13). By the late 1940s I had abandoned end-to-end anastomosis for an established stricture, particularly the

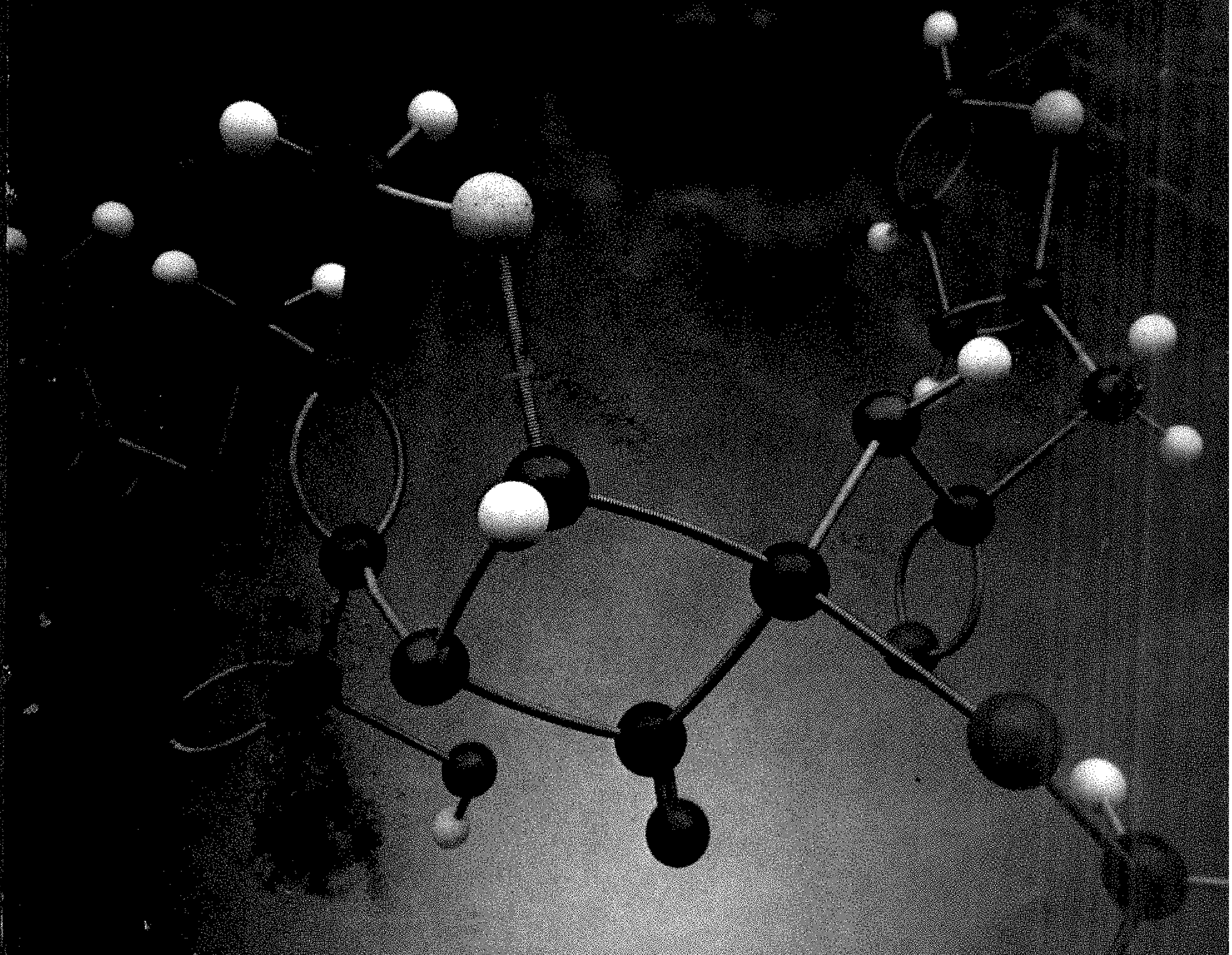
MSD announces
the discovery of

Mefoxin®

Cefoxitin sodium, MSD

INJECTION

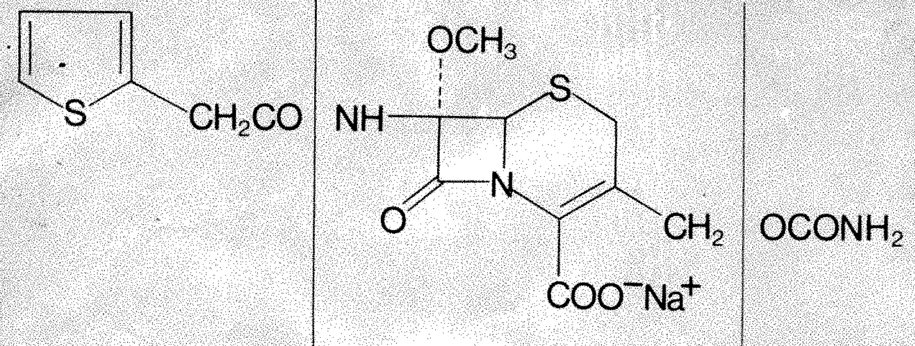
First of the cephamycins



A new class of antibiotics

'Mefoxin' is derived from cephamycin C, a naturally occurring antibiotic substance produced by *Streptomyces lactamdurans*. This naturally occurring antibiotic has been modified in the MSD Research Laboratories to enhance its therapeutic usefulness.

'Mefoxin' has a unique mol[illegible] e offering outstanding clinical benefits [illegible]nd a [illegible]ecif clinical profile.



Thienylacetyl side-chain:

enhances activity against Gram-positive pathogens

Cephamycin nucleus:

provides bactericidal activity against a wide range of pathogens, Gram-negative in particular. 7α-methoxy group protects against β-lactamase degradation

Carbamo side-chai

protects antibiotic metabolised

▼Prescribing information

Indications

'Mefoxin' is a broad-spectrum bactericidal antibiotic indicated for the treatment of infections caused by susceptible strains of Gram-positive and Gram-negative pathogens both aerobic and anaerobic.

'Mefoxin' has been clinically effective not only in infections due to antibiotic-sensitive organisms, but also in infections due to organisms resistant to one or more of the following antibacterial agents: penicillin, ampicillin, carbenicillin, tetracyclines, erythromycin, chloramphenicol, cephalosporins, kanamycin, gentamicin, tobramycin, and sulphamethoxazole-trimethoprim.

Many Gram-negative pathogens are resistant to penicillins and cephalosporins through the action of the β-lactamases which are produced by these pathogens. 'Mefoxin' is remarkably stable in the presence of these bacterial β-lactamases, both penicillinases and cephalosporinases. Hence, the clinical efficacy of 'Mefoxin' extends to many infections caused by such pathogens.

'Mefoxin' is indicated for the treatment of the following infections caused by sensitive bacteria
Peritonitis and other intra-abdominal and intrapelvic infections; female genital tract infections; septicaemia; urinary tract infections; respiratory tract infections; bone and joint infections; and skin and soft-tissue infections.

'Mefoxin' is indicated for adjunctive therapy in the surgical treatment of infections, including abscesses, infection complicating hollow visceral perforations, cutaneous infections, and infections of serous surfaces, whether caused by aerobes, mixed aerobes and anaerobes, or anaerobes.

Microbiology

'Mefoxin' is active *in vitro* against

Aerobic bacteria

Gram-positive cocci including *Staphylococci* (including coagulase-positive, coagulase-negative, and penicillinase-producing strains); Group A beta-haemolytic streptococci *(Streptococcus pyogenes)*; Group B beta-haemolytic streptococci *(Streptococcus agalactiae)*; *Streptococcus pneumoniae (Diplococcus pneumoniae)*; other streptococci (except group D streptococci including enterococci, most strains of which are resistant, e.g. *Streptococcus faecalis*) *Gram-negative cocci including* *Neisseria gonorrhoeae* (including penicillinase-producing strains), *Neisseria meningitidis* *Gram-negative rods (facultative anaerobes) including* *Escherichia coli, Klebsiella pneumoniae*, Klebsiella spp., *Proteus mirabilis* *Proteus* (indole-positive) *Proteus vulgaris, Proteus rettgeri, Proteus morganii, Haemophilus influenzae, Serratia marcescens*, Providencia spp., Salmonella and Shigella spp.

Anaerobic bacteria

Gram-positive cocci including Peptococcus spp.; Peptostreptococcus spp., Micro-aerophilic streptococcus *Gram-positive rods including* *Clostridium perfringens*, Clostridium spp., Eubacterium spp., *Propionibacterium acnes*. *Gram-negative cocci including* Veillonella spp. *Gram-negative rods including* *Bacteroides fragilis, Bacteroides melaninogenicus*, Bacteroides spp. (including both penicillin-susceptible and penicillin-resistant strains) Fusobacterium spp.

'Mefoxin' is active against some strains of the following bacteria: *Acinetobacter calcoaceticus* var *anitratum (Herellea vaginicola)*, *Acinetobacter calcoaceticus* var *lwoffi (Mima polymorpha)*, *Alcaligenes faecalis*, Citrobacter spp. and Flavo-bacterium spp., Enterobacter spp.

'Mefoxin' is not active against Pseudomonas, most strains of enterococci and many strains of *Enterobacter cloacae*.

Dosage and administration

'Mefoxin' may be administered intravenously or intramuscularly. (See reconstitution directions for each route below.) Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organisms, and condition of the patient.

Therapy may be started while awaiting the results of susceptibility testing.

Dosage. The usual adult dosage is 1 g or 2 g of 'Mefoxin' every eight hours. (See chart.)

In adults with renal insufficiency, an initial loading dose of 1 g or 2 g may be given. After a loading dose, the following recommendations for *maintenance dosage* may be used as a guide.

Usual adult dosage

Type of infection	Dose	Fr
Uncomplicated	1 g	Ev (o ev
Moderately severe or severe	2 g	Ev (x ev
Infections generally needing antibiotics in higher dosage	3 g (2 g)	Ev (E

Maintenance dosage of 'Mefoxin' in renal function

Renal function	Creatinine clearance (ml min)	
Mild impairment	50-30	
Moderate impairment	29-10	
Severe impairment	9-5	(
Essentially no function	<5	(

In the patients undergoing haemodialys 2 g should be given after each haemod dose should be given as indicated in th

Intravenous administration: reconstitut Injection BP. 1 g is soluble in 2 ml. Alth soluble, for intravenous use it is prefera Injection BP to the 1 g vial or the 2 g via withdraw entire contents of vial into sy

For direct intravenous injection, 'Mefox

Out[illegible] [illegible]ical benefits

Wide-ranging activity ag[illegible] [illegible]ram-ne[illegible]ative and Gram-positive pathogens, anaerobes a[illegible] [illegible]as aerobes.

Unusually high resis[illegible] [illegible]-lactamase degradation.

Highly active against [illegible]oides *fragilis* and strains of *E. coli*, Serratia, Klebsiella spp. and Proteus spp. (including indole positive strains) resistant to other antibacterial agents.

Offers high levels of active antibiotic in the body.

A record of relative safety comparable to the penicillins.

Prime indications include:

- Peritonitis, and other intra-abdominal and intrapelvic infections.
- Female genital tract infections
- Septicaemia
- Skin and soft tissue infections
- Bone and joint infections
- Urinary tract infections
- Respiratory tract infections (e.g. inhalation pneumonia)

Specific clinical profile

'Mefoxin' is exceptionally valuable wherever Gram-negative pathogens and anaerobes are involved in mixed infections. When mixed infections are suspected, therapy may be started while awaiting the results of susceptibility testing.

Mefoxin®

First of the cephamycins

the vein over a period of 3 to 5 minutes or may be given through the tubing when the patient is receiving parenteral solutions.

An intermittent intravenous infusion of 'Mefoxin' may be employed when large amounts of fluid are to be given. However, during infusion of the solution containing 'Mefoxin' it may be advisable temporarily to discontinue administration of any other infusion solution at the same site (by using an appropriate IV infusion set).

A solution of 'Mefoxin' may also be given by continuous intravenous infusion (see below for compatibility and stability).

Intramuscular administration ONLY

Reconstitute 'Mefoxin' 1 g with 2 ml of Water for Injection BP or 0.5% or 1% lignocaine hydrochloride (without adrenaline) solution. 'Mefoxin' is given by deep injection into a large muscle mass. Avoid injection into a blood vessel.

Compatibility and stability

A solution of 'Mefoxin' in Water for Injection BP may be added to the following solutions: 0.9% Sodium Chloride Injection BP, 5% or 10% Dextrose Injection BP, Dextrose and Sodium Chloride Injection (5%/0.9%, 5%/0.45%, or 4.3%/0.18%), Lactated Ringer's Injection USP, 5% Dextrose in Lactated Ringer's Injection, 5% or 10% invert sugar in water, 10% invert sugar in saline solution, 4.2% Sodium Bicarbonate Injection BP, M/6 Sodium Lactate Injection BP.

'Mefoxin', as constituted to 1 g/10 ml with Water for Injection BP, Water for Injection BP preserved with parabens or benzyl alcohol, 0.9% Sodium Chloride Injection BP or 5% Dextrose Injection BP maintains satisfactory potency for 24 hours at room temperature, for 96 hours under refrigeration, and for 13 weeks in the frozen state.

'Mefoxin' can be administered concomitantly with such antibiotics as gentamicin, tobramycin, carbenicillin or amikacin. When 'Mefoxin' is administered with another antibiotic, they should not be mixed in the same syringe.

Contra-indications

'Mefoxin' is contra-indicated in persons who have shown hypersensitivity to cefoxitin. In the absence of clinical experience, 'Mefoxin' should not be administered to patients who have shown hypersensitivity to cephalosporins.

Precautions

There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and other β-lactam antibiotics, penicillins, and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most β-lactam antibiotics.

Before therapy with 'Mefoxin', careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibiotics. 'Mefoxin' should be given cautiously to penicillin allergic patients.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. If an allergic reaction to 'Mefoxin' occurs, the drug should be discontinued.

The total daily dosage should be reduced when 'Mefoxin' is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see 'Dosage and administration') because high and prolonged serum antibiotic concentrations can occur from usual doses.

Interference with laboratory tests

A false-positive reaction to glucose in the urine may occur with reducing substances but not with the use of specific glucose oxidase methods.

Use in pregnancy

Use of the drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the foetus due to 'Mefoxin'. There are no controlled studies with 'Mefoxin' in pregnant women.

Nursing mothers

'Mefoxin' is excreted in human milk.

Infants and children

Pending the outcome of clinical trials in progress, the conditions for use of 'Mefoxin' in infants and children remain to be defined.

Side effects

'Mefoxin' is generally well tolerated. Side effects rarely require stopping treatment and [illegible]

Local reactions

Thrombophlebitis has occurred with intravenous [illegible]. Pain, induration and tenderness after intramuscular [illegible] have been reported.

Allergic

Maculopapular rash [illegible] allergic reactions have been noted rarely.

Gastro-intestinal

Diarrhoea has been reported rarely.

Blood

Transient leucopenia and [illegible]. Some individuals, particularly [illegible] may develop positive direct Coombs tests during therapy with 'Mefoxin'.

Liver function

Transient elevations [illegible] alkaline phosphatase have been reported rarely.

Kidney

Elevations in serum creatinine and/or [illegible] have been observed. The role of 'Mefoxin' in changes [illegible] is difficult to assess, since factors predisposing [illegible] or to impaired renal function usually have been [illegible]

Presentation

In vials containing 1 g or 2 g [illegible] gram of cefoxitin contains approximately [illegible]

Product licence numbers [illegible]

Product authorisation numbers [illegible]

Issued October 1978

Additional information is available to the medical [illegible] on request.

Basic NHS cost [illegible]

Merck Sharp & Dohme Limited,
Hoddesdon, Hertfordshire EN11 9BU

* denotes registered trademark

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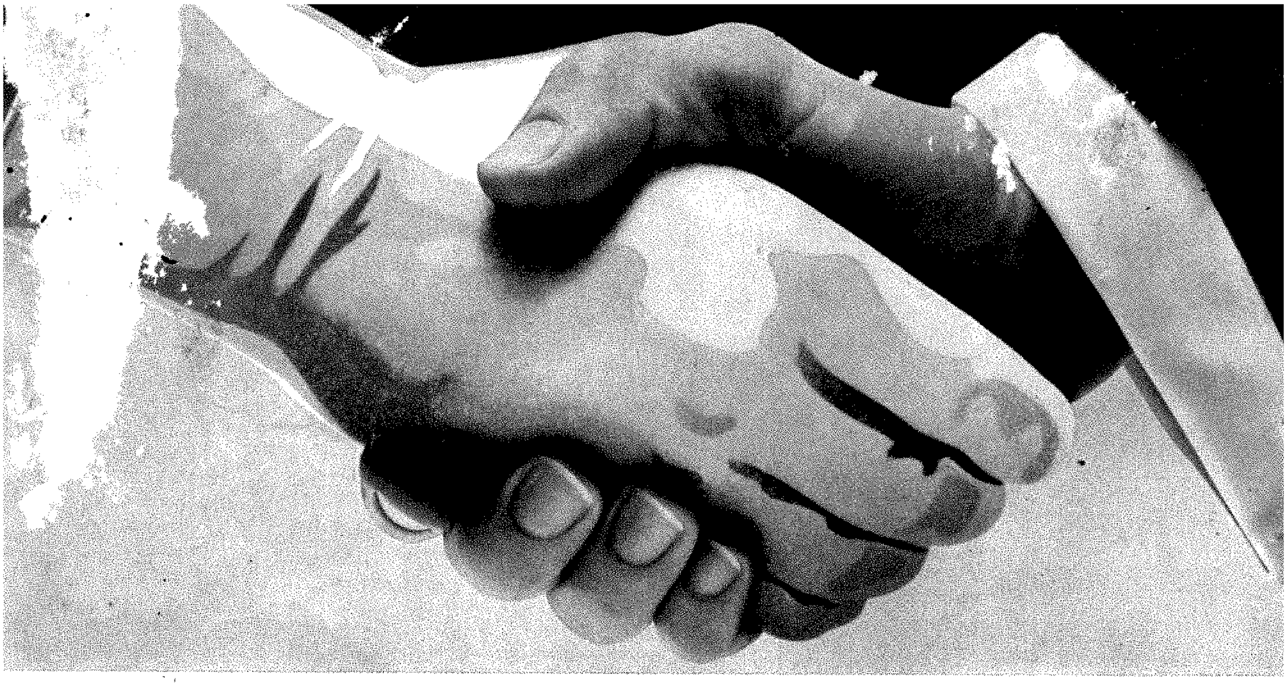

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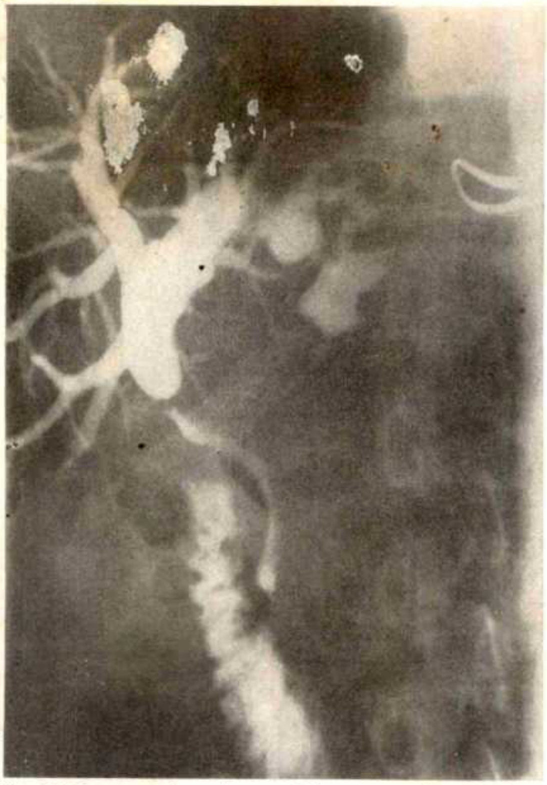


Fig. 11. Postoperative stricture of the common hepatic duct, but enough duct remains above the lesion for end-to-end anastomosis to be performed.

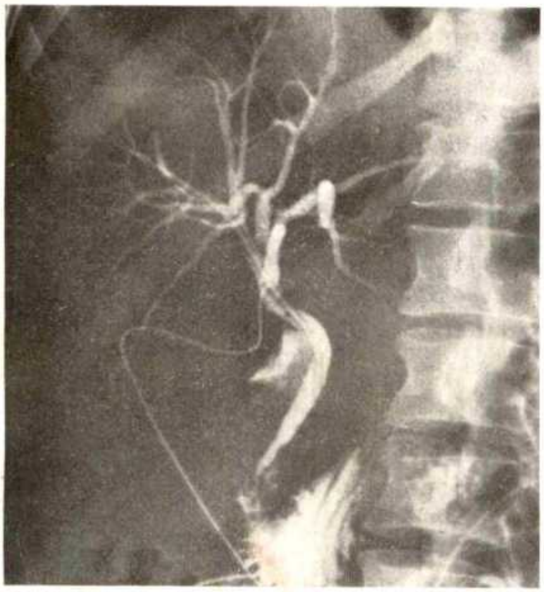


Fig. 12. End-to-end anastomosis of a damaged bile duct, splinted by a T tube placed in the duct through a separate incision.

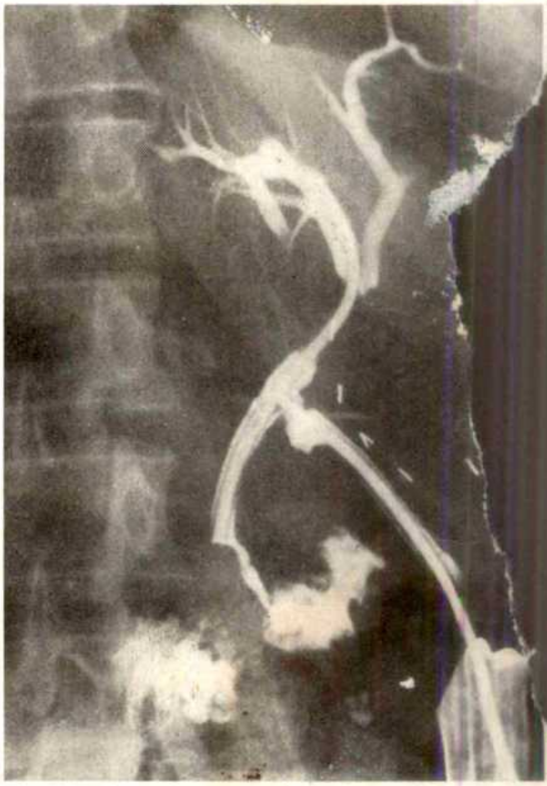


Fig. 13. End-to-end anastomosis of a damaged bile duct, splinted by a T tube. Postoperative cholangiogram showing that if the anastomosis is performed under tension, the ends will separate.

very high hilar stricture (*Fig.* 14), in favour of hepaticojejunostomy, employing a Roux loop (*Fig.* 15) (Smith, 1964a). I continued to use a temporary indwelling tube as a stent and in 1949, for the first time, I used, instead of a T tube from below, a straight length of tube running transhepatically (*Fig.* 16). I described 15 years' experience with the transhepatic tube in 1964 (Smith 1964b), and quite soon it became apparent from publications that other surgeons favoured a tube inserted in this way, some of them having clearly come to this decision independently, in particular Praderi of Montevideo, to whose thoughtful papers I would pay tribute (Praderi, 1974; Praderi, Delgado et al., 1974; Praderi, Mazza et al., 1974).

The results of hepaticojejunostomy splinted by a transhepatic tube were an improvement upon end-to-end anastomosis, but nevertheless I was disappointed to find that there were still too many failures for any degree of satisfaction. Those due to established biliary cirrhosis one could understand, but in those cases in which a favourable result was expected, some 25 per cent returned with evidence of restenosis at the site of the anastomosis. Why, I asked myself, should the anastomosis restenose after removal of the transhepatic tube, even if this had been left *in situ* for 6 or even 12 months? I came to the conclusion that, at least in the very high recurrent hilar stricture, the reason

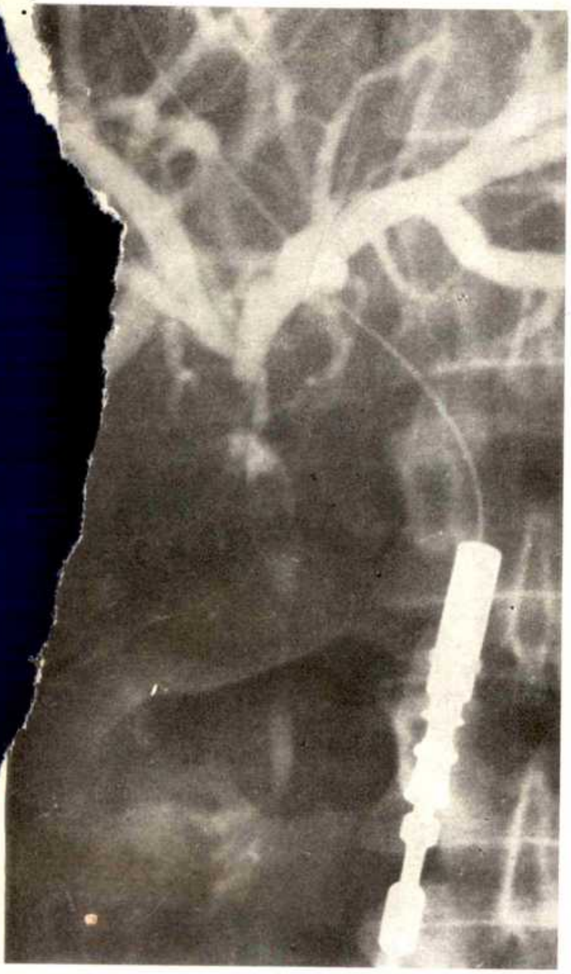


Fig. 14. Transhepatic cholangiogram showing a high hilar stricture of the common hepatic duct and also that a gallbladder remnant containing stones is still present.

probably lay in the impossibility of achieving, with a traditional sutured anastomosis, an adequate apposition of the bile duct epithelium and jejunal epithelium.

As I wrote in 1972

> Trauma to the bile duct during cholecystectomy often does occur at a very high level. Moreover, if the injury leaves, say, half a centimetre of common hepatic duct below the liver, this half centimetre of usable common hepatic duct may disappear as a result of repeated unsuccessful attempts at repair. It is thus far from uncommon for a surgeon to explore a stricture of the bile duct and to find that the normal criteria for success cannot possibly be achieved, and that in particular it does not appear possible to appose accurately the lining of the common hepatic duct above the stricture either to the lining of the distal duct below or to the epithelium of a loop of jejunum brought into the porta hepatis. It is little use in these cases to core out of the thickened capsule of the liver a cylinder of scar tissue and to call this a duct, for anastomosis of a cylinder of scar tissue without an epithelial lining to the jejunum, whilst it will serve for a while, is bound to restenose at a later date.

It seemed to me that if access to the epithelial lining of the bile duct is so inadequate through the mass of scar tissue in the porta hepatis that accurate suture to the epithelial lining of the jejunum appears to be impracticable, a successful repair could still be achieved if in some way the epithelial lining of the jejunum could be placed through the zone of fibrosis and in contact with the duct lining. This is the principle of the 'mucosal graft' operation, which I introduced into my practice 10 years ago (Smith, 1969, 1972) (*Figs.* 17–19). It is effected by cutting away a disc of the seromuscular coat of the jejunum in order to expose the mucosa and make a diverticulum which can be used as a mucosal graft to line the area where the epithelium is missing. A variety of methods have been employed in order to place this graft *in situ.*

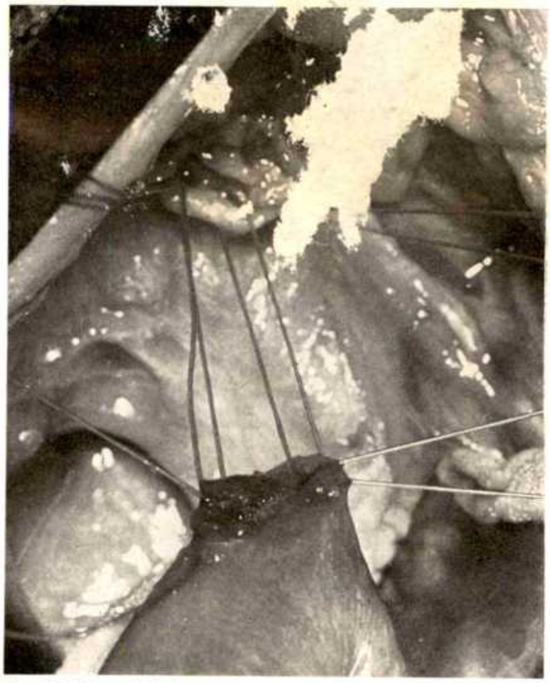
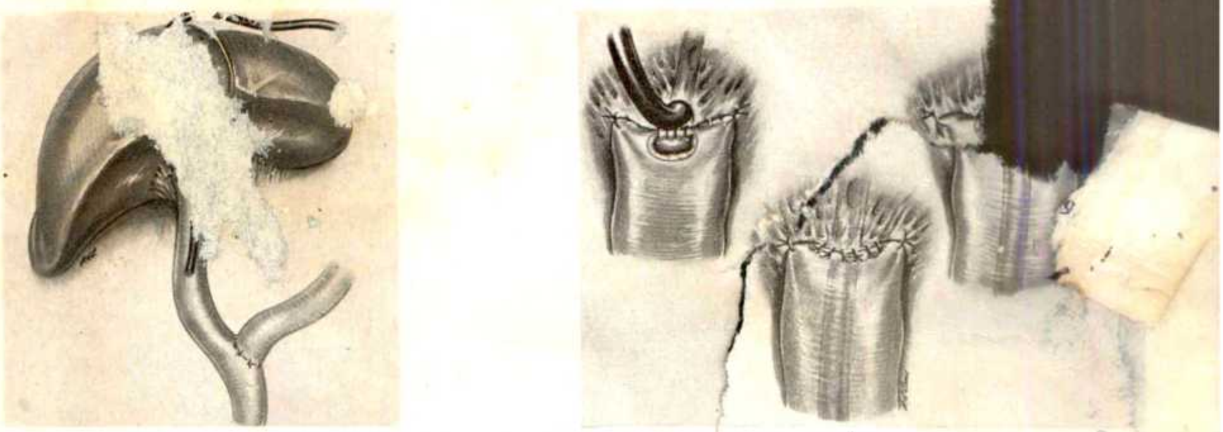


Fig. 15. Hepaticojejunostomy: magnified view of the first sutures placed between the common hepatic duct and jejunum. This operation will not succeed unless jejunal and duct epithelium can be apposed without tension.

Initially a specially constructed Y tube was employed which, with its two limbs inserted into right and left hepatic ducts, carried the jejunal mucosa up into contact with the epithelial lining of the hepatic duct system, the tube later dropping out into the jejunum and being passed per rectum (*Fig.* 17*c*). This was a stage of transition and led on to a technique employing both a mucosal graft and a transhepatic tube, the graft ensheathing and being attached to the tube so that the sleeve of jejunal mucosa is drawn up through the scar tissue around the duct and well into the intrahepatic duct system (*Fig.* 18).

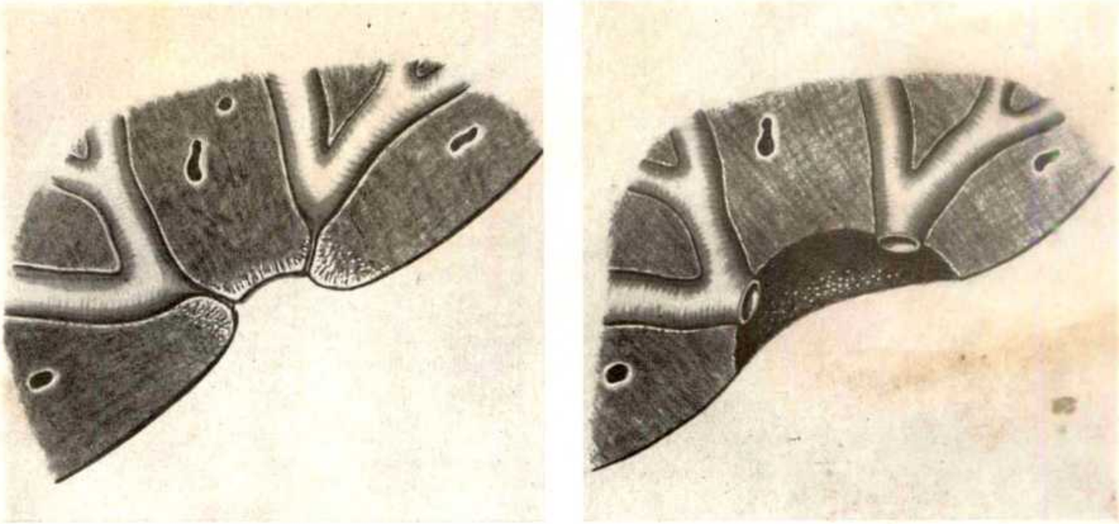
No sutures are used in the junction of hepatic duct epithelium and jejunal epithelium but the weight of the Roux loop is supported by suturing it t thickened capsule of the liver around the du Redivac drain is placed below the liver adjacer anastomosis and usually a second Redivac positioned below the diaphragm where the hepatic tube emerges from the dome of the liver.

Postoperatively, the transhepatic tube is attached to a low tension electric pump. Suction is discontinued



a *b*

Fig. 16. Hepaticojejunostomy for a high stricture, splinted by a transhepatic tube.



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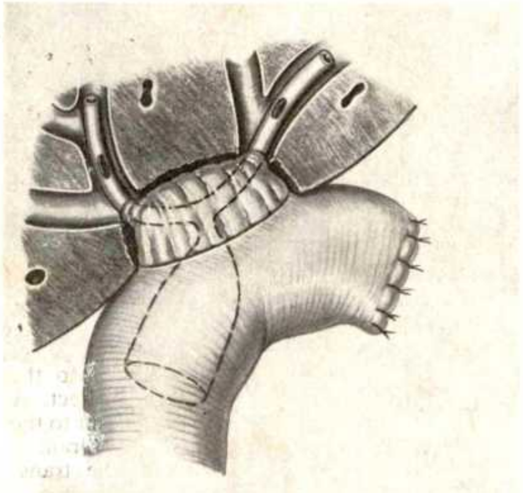

c

Fig. 17. Mucosal graft replacement of totally excised common hepatic duct.

as soon as bile ceases to be recovered from the Redivac tubes, which are then removed. The transhepatic tube is then allowed to drain freely into a bag and after 7–10 days is spigotted. The patient is discharged home after 12–14 days, having been taught to wash the tube through once daily with sterile water or saline. Four months postoperatively the patient is readmitted to hospital for 48 h for a general assessment, including a tube cholangiogram, bacteriological examination of bile and liver function tests, after which the tube is removed (*Figs.* 18–19).

It is my belief that the combination of the mucosal graft with a transhepatic tube is a useful one for the following reasons:

1. However high the ductal injury, the mucosa of the jejunum can be placed in contact with the epithelial lining of the hepatic duct system.
2. Splinting the junction of duct to jejunum with an indwelling tube is probably useful and the transhepatic tube can be left in as long as is desired.

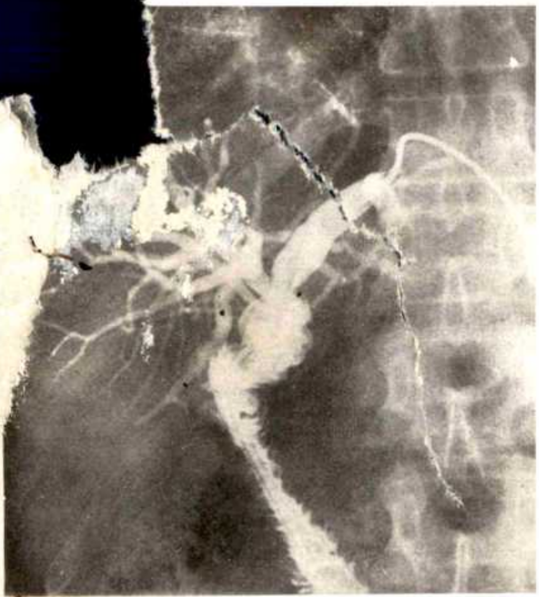

Fig. 18. Repair of hepatic duct stricture with mucosal graft and transhepatic tube (postoperative tube cholangiogram).

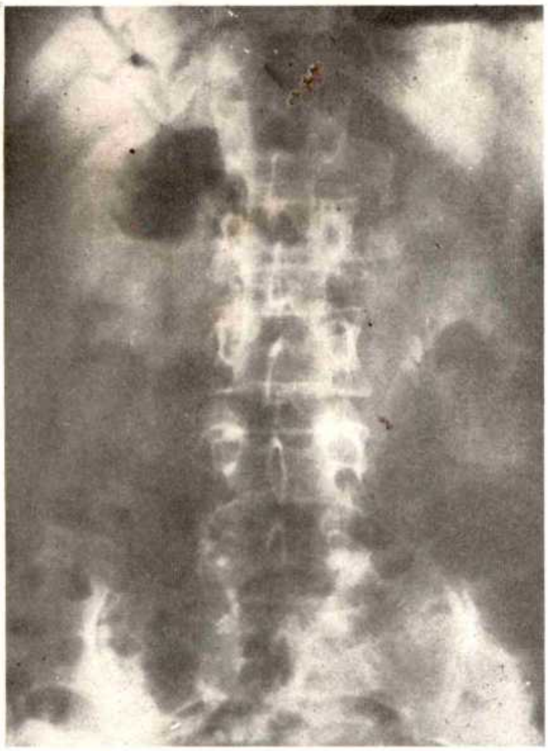

Fig. 19. Repair of hepatic duct stricture with mucosal graft and transhepatic tube ('Pepsicologram' 1 year later).

3. The only stitches employed are those anchoring the Roux loop to the capsule of the liver, and the junction of bile duct epithelium to jejunal epithelium is sutureless.

4. Diversion [illegible] n is achieved in the p[illegible] ative [illegible] ing the transhepatic tu[illegible] a lo[illegible] amp.

5. The transhep[illegible] tube [illegible] duct system to be washed out pos[illegible] eratively as well as at operation. It further allows radiological studies (*Figs.* 18, 19) and permits bile to be taken for culture whenever desired.

In the case of a duct injury so high that no common hepatic duct remains, the right and left hepatic ducts being identified separately, two transhepatic tubes are employed, both attached to the same jejunal mucosal pocket. This is also the technique of reconstruction employed after resection of a carcinoma of the common hepatic duct.

Results

Repair of a bile duct stricture employing the mucosal graft technique is simpler and easier to perform than repair employing a standard suture technique and it takes considerably less time. This is reflected in the operative hazard. Nearly 600 operations of this kind have now been performed, the last 227 without mortality.

The percentage of patients permanently cured is more difficult to assess, for how are we to measure what is permanent? Following other techniques patients return with recurrence of trouble 2, 5, even 20 (in one case) years later and we have no right to assume that this will prove different after a mucosal graft operation.

Analysis of the results of all patients after a mucosal graft operation for whom reliable records were available 2 years postoperatively showed the following: 85 per cent were anicteric and without symptoms, divided into 45 per cent with normal liver function tests and 40 per cent with abnormal liver function tests (usually an elevated serum alkaline phosphatase); 11 per cent had unsatisfactory results which had been anticipated at operation on account of (*a*) a long history and established biliary cirrhosis, or (*b*) a long history and secondary sclerosing cholangitis with multiple intrahepatic ductal strictures, or (*c*) a long history and severe chronic purulent cholangitis with multiple intrahepatic calculi; 4 per cent had restenosis where a favourable result had been anticipated (all of these have been or will be reoperated upon and the odds favour a final successful result).

In that the great majority of patients suffering restenosis of a hepatico-jejunal anastomosis present evidence that this is taking place during the first year after operation, these 2-year figures suggest that with a mucosal graft type of repair restenosis becomes an uncommon cause of an unsatisfactory result. No technique is likely ever to eliminate restenosis altogether or solve the problem of the liver already damaged beyond repair. Here a new donor liver would seem to be the only hope.

I cannot end this evening without expressing not only my gratitude that I should have been accorded the very great honour of being allowed to deliver a lecture commemorating the name of that very great surgical pioneer, Sir William Macewen, in a university and city which has in many other ways contributed so greatly to British and to world surgery, but also my sense of extreme pleasure and personal enjoyment that I should find myself delivering this lecture before so many old friends and colleagues. It has been for me an occasion I shall never forget.

Ref[illegible]

CAT[illegible] [illegible]gn st[illegible] of the biliary duc[illegible]

LONGMI[illegible] M. C. ([illegible]) Intrahepatic cholangiojejunostomy for[illegible] v obst[illegible]on. Further studies. *Ann. Surg.* **130**, 455–46[illegible]

MAINGOT R. (1977) Postoperative strictures of the bile ducts. Causes, prevention, repair procedures. *Br. J. Clin. Pract.* **31**, 117–126.

PRADERI R. C. (1974) Twelve years' experience with transhepatic intubation. *Ann. Surg.* **179**, 937–940.

PRADERI R., DELGADO B., MAZZA M. et al. (1974) Drainages trans-hépatiques doubles. *Lyon Chir.* **70**, 294–298.

PRADERI R., MAZZA M., GOMEZ C. et al. (1974) Le drainage transhépatique en séton. *Presse Méd.* **3**, 2015–2018.

SMITH R. (1964a) Hepaticojejunostomy: [illegible] ostomy. A method of intrajejunal ana[illegible] *Surg.* **51**, 183–186.

SMITH R. (1964b) Hepaticojejunostomy w[illegible] intubation. A technique for very high [illegible] hepatic ducts. *Br. J. Surg.* **51**, 186–194.

SMITH R. (1969) Strictures of the bile ducts. [illegible] **62**, 131–137.

SMITH R. (1972) Stricture of the bile ducts. I[illegible] BROOKE B. N. (ed.) *Recent A[illegible]* 2nd ed. Edinburgh, Churchill [illegible]

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[illegible] infusion in experimental refractor[illegible]

S[illegible]ITH AND J. N. NORMAN*

[illegible] contribution of primary myocardial [illegible] the [illegible]athogenesis of refractoriness of shock to [illegible]ional therapy is in direct contradiction to the [illegible]ly advocated clinical practice of infusion of large [illegible]mes of fluid in shock resuscitation. A standard [illegible]ine haemorrhagic shock model, in which refractory [illegible]ck is induced by maintaining an arterial blood [illegible]ssure of 40 mmHg for 2 h, has been used to assess [illegible] effects of volume infusion to maintain a central [illegible]ous pressure of 0–2 mmHg for a further 2 h and [illegible]he tolerance of such an infusion by the heart in refractory shock.

Fluid infusion ensured significantly better figures for oxygen balance than in those animals where additional fluid was not given, and the volumes required appeared to be well tolerated by the shocked myocardium.

Primary myocardial failure does not appear to be a major aetiological factor in refractory shock, and provided that the usual monitoring parameters are recorded, volume infusion remains a major part of shock resuscitation.

A NUMBER of theories have been advanced to explain the resistance to conventional therapy of certain patients in severe shock. Wiggers, in 1942, was one of the first to suggest a role for primary myocardial failure, and since then other workers have not only supported a primary myocardial contribution but have also identified a myocardial depressant factor, believed to be elaborated by the ischaemic pancreas (Brand and Lefer, 1966).

It has been well established, however, that in the resuscitation of severe shock, adequate volume infusion is essential, usually requiring infusion of fluid, in addition to blood transfusion, in volumes up to two or three times the estimated blood volume (Harkins, 1941; Hunt, 1972).

The basic 'Wiggers' model failed to take account of this clinical phenomenon and the discrepancy between experimental and clinical facts seemed worthy of fuller evaluation.

Methods

Adult dogs were fasted overnight, anaesthetized with sodium pentobarbital 25 mg/kg body weight, intubated and allowed to breathe room air spontaneously. Using a clean but non-sterile technique, both femoral vessels bilaterally were isolated and cannulated. This allowed monitoring of mean aortic and central venous pressures, assessment of cardiac output by the dye dilution method, withdrawal of arterial blood samples and arterial haemorrhage into a heparinized reservoir. On insertion of the first cannula, total heparinization was ensured by injection of a solitary bolus of 0·3 mg/kg body weight. A Swan–Ganz catheter was inserted into the pulmonary artery via the right jugular vein to monitor pulmonary artery pressure and to obtain venous blood samples.

Oesophageal temperature was monitored throughout and core temperatures maintained at 37±2 °C by a simple heat cage. An electrocardiograph was recorded continuously via subcutaneous electrodes.

Once stability of the preparation was confirmed (*see below*), refractory shock was induced by arterial haemorrhage to maintain mean aortic press[illegible] mmH[illegible]t a 2-h hypotensive period. Initi[illegible] this involv[illegible]s withdrawal of blood through a Watson–Ma[illegible]pump, the maximum bleed-out volume being rea[illegible] after 75–90 min (Wiggers et al.. 1948). Thereafter, decompensation of the microcirculation began and reinfusion from the reservoir was essential to avoid too severe a reduction in pressure (Wiggers and Ingraham, 1946). At the end of 2 h the remaining reservoir blood was reinfused and the animals were allocated randomly to one of two groups. In one group (10 dogs) no additional fluid was reinfused, i.e. the classic Wiggers model; in the other (15 dogs) functional normovolaemia was ensured by infusion of sufficient of a standard colloid/crystalloid perfusate to maintain central venous pressure at 0–2 mmHg. Observations were continued for a further 2 h, after which the animals were sacrificed.

The perfusate used consisted of a mixture of saline, Dextran 40 (40 ml/l) and Dextran 70 (340 ml/l) with added calcium chloride (2·7 mmol/ml) and potassium chloride (8·0 mmol/l) and the solution was buffered to pH 7·30±0·05.

To ensure that the preparation was stable, at least twice before haemorrhage and at 15-min intervals during the experiment, measurements were made of cardiac output, of mean aortic, central venous and pulmonary artery pressures and of temperature and heart rate. Arterial and mixed venous blood samples were obtained for blood-gas analysis (partial pressures and total content), acid base, haemoglobin, haematocrit and lactate estimations. From these it was possible to calculate stroke volume by dividing cardiac output by pulse rate; total peripheral resistance by dividing arterial pressure by cardiac output; oxygen availability as the product of cardiac output and arterial oxygen content; and consumption as a product of cardiac output and arteriovenous oxygen difference. By plotting oxygen consumption graphically and relating the individual figures to a zero of the resting value of 100 per cent, it was possible to calculate an oxygen debt when the figures were below zero and attempted repayment of the debt when the figure was greater than 100 per cent. By calculating the areas below each curve a cumulative figure of oxygen balance could be obtained (*Fig* 1). In those animals given no additional fluid initially, 500 ml of Dextran 70 were infused over 15 min at the end of a 4-h study and the cardiovascular parameters were remeasured after a further 15 min before sacrifice.

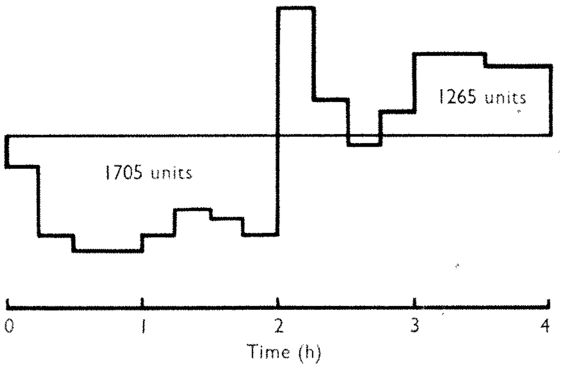

Fig. 1. Oxygen balance in dogs given blood plus perfusate.

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Results

The mean resting v[illegible] was computed at 100 per cent and all other [illegible] tained were expressed as a percentage of [illegible] ight results for each parameter in [illegible] e obtained and these have been p[illegible] figure for each of the 2-h perio[illegible] plus or minus the standard error of the m[illegible] tical analysis was performed by the Student [illegible] paired or unpaired data as appropriate.

As shown in *Table I*, both groups were comparable as regards mean body weight, maximum bleed-out volume and the proportion of the maximum bleed-out volume reinfused to avoid too severe hypotension during the 2-h hypotensive period. The dogs given additional fluid required a mean volume of 89·16 ± 10·15 ml/kg to ensure a positive central venous pressure of 0–2 mmHg throughout the 'recovery' phase.

Hypotensive phase: Both groups demonstrated similar haemodynamic and biochemical changes during the 2-h hypotensive period. Both cardiac output (16·04 ± 0·87 per cent) and stroke volume (14·20 ± 1·17 per cent) were reduced from a resting value of 100 per cent. There was a twofold increase in total peripheral resistance (204·17 ± 9·19 per cent). There was a reduction in oxygen availability and a less marked decrease in total oxygen consumption (15·24 ± 0·76, 63·88 ± 3·67 per cent, respectively), resulting in a cumulative oxygen debt of −2649 arbitrary units. There was a progressive, sustained increase in arterial lactate (800·89 ± 43·19). pH, $P\mathrm{o}_2$, $P\mathrm{co}_2$ and bicarbonate mirrored the changes described and have not been reported in detail.

'Recovery' phase (*Table II*)

Following reinfusion of blood, the dogs given no additional perfusate showed sub-resting values for central venous pressure, had persisting tongue cyanosis and were considered to be hypovolaemic. The group reinfused with blood alone demonstrated a persistently reduced cardiac output (52·24 ± 5·10 per cent) and stroke volume (49·09 ± 5·33 per cent) with an associated increase in peripheral resistance (121·71 ± 6·56 per cent). Mean oxygen availability (57·35 ± 6·56 per cent) was below the resting value of 100 per cent. Mean oxygen consumption was 95·58 ± 3·22 per cent of resting and the cumulative oxygen debt increased to −4007 units after a further 2 h.

In the group given additional perfusate to restore functional normovolaemia, the results were quite different. Cardiac output was increased to 186·62 ± 7·91 per cent and stroke volume to 196·33 ± 10·82 per cent of resting. Total peripheral resistance was reduced to a mean of 57·92 ± 2·90 per cent, all three differences being significant relative to the group given blood alone (P < 0·001).

Mean values for oxygen availability (127·17 ± 16·26 per cent) and consumption (121·98 ± 6·56 per cent) were significantly higher (P < 0·001) and the oxygen debt was significantly lower (−440 units).

Table I: BODY WEIGHTS, SEVERITY O[illegible] S[illegible] AND REQUIREMENTS FOR FLUID INF[illegible]

	Mean body weight (kg)	Max bleed-out volume (% blood vol.)	Vol[illegible] reinfu[illegible] (% m[illegible] ble[illegible] vo[illegible]	[illegible]
Blood only	16·34 ± 0·65	59·20 ± 2·77	21·5[illegible] 3·6[illegible]	[illegible]
Blood plus perfusate	17·72 ± 1·34	51·6 ± 6·00	36·17 ± 7·[illegible]	8[illegible]·16 10·[illegible]

Values are given ±s.e. mean.

Table II: REFRACTORY PHASE: 2 h FOLLOWING REINFUSION

	Blood only	Blood + perfusate
Cardiac output	52·24 ± 5·10	186·62 ± 79·1*
Stroke volume	49·09 ± 5·33	196·33 ± 10·82*
Total peripheral resistance	121·71 ± 3·94	57·92 ± 2·90*
Oxygen availability	57·35 ± 6·56	127·17 ± 16·27*
Oxygen consumption	95·58 ± 3·22	121·98 ± 6·56*
Total oxygen debt	−4007 units	−440 units
Arterial lactate	765·25 ± 65·52	787·97 ± 69·58
Haemoglobin	112·49 ± 0·17	69·18 ± 4·61*
Haematocrit	114·62 ± 0·23	68·52 ± 5·59*

Mean results ± s.e. mean expressed as percentage of resting value (resting value, 100 per cent).
Statistical analysis by the Student t test for paired data:
* P < 0·001.

Table III: DOGS GIVEN RESERVOIR BLOOD ONLY FOLLOWING INFUSION OF DEXTRAN 70

	Hypotensive	Refractory	After 500 ml Dextran 70
Cardiac output	16·04 ± 0·87	52·23 ± 5·10	134·14 ± 9·06*
Stroke volume	14·20 ± 1·17	49·09 ± 5·33	143·9 ± 7·63*
Total peripheral resistance	204·17 ± 9·19	121·71 ± 3·94	53·22 ± 2·23**

Mean results expressed as percentage of resting value ± s.e. mean, the initial resting value being taken as 100.
Statistical analysis by the Student t test for paired data:
* P < 0·0001; ** P < 0·002.

Effect of infusion of Dextran 70 (*Table III*)

In the group given blood alone for the 2-hour recovery phase, the effect of an infusion of 500 ml of Dextran 70 at the end of the experiment was studied and parameters assessed after a further 15 min. Cardiac output was increased to 134·14 ± 9·06 per cent and stroke volume to 143·90 ± 7·63 per cent of the resting value, the difference between these and the results before infusion of Dextran 70 being significant (P < 0·001). Total peripheral resistance was significantly reduced (53·22 ± 2·23 per cent —) from the 121·71 ± 3·94 per cent before infusion of the Dextran 70 bolus (P < 0·002). This figure was not significantly different from the 57·92 ± 2·90 per cent resting value shown in the group given additional perfusate throughout the recovery period.

Discussion

The effects of haemorrhage seen during the 2-h hypotensive period are well established both experimentally and clinically. Initially, consequent upon the reduced venous return, there was a reduction in both cardiac output and stroke volume. Hypovolaemia stimulated catecholamine release (Longerbeam et al., 1960) which in turn produced marked peripheral vasoconstriction as demonstrated by a twofold increase in total peripheral resistance. Adrenergic stimulation produced chronotropic cardiac stimulation with significant tachycardia.

Because of lowered cardiac output and peripheral vasoconstriction peripheral perfusion was impaired, with interference in capillary flow and transport of nutrients, including oxygen (Appelgren and Lewis, 1970). In response to hypoxia there was interference with cellular metabolic function and a transfer to anaerobic energy production. This has been confirmed in the present study by an increasing acidosis and an eightfold increase in arterial lactate.

Control of the microcirculation has been shown to be dependent on local oxygen levels (Stalker, 1970) and to be adversely affected by local acidosis and accumulation of metabolites. In response to severe hypoxia, more and more of the capillary field has become dilated with further embarrassment of cellular nutrition. As the hypoxic insult persisted, disruption of cellular microstructure began with the release of deleterious lysosomal enzymes, which in turn aggravated the interference in cellular and visceral function (Baue, 1968).

The point at which this process becomes irreversible has not been clearly defined, but might be the point at which reinfusion of blood from the reservoir became essential to avoid too severe hypotension (Wiggers and Ingraham, 1946). If not reversed, persistent hypoxia and acidosis would contribute to the disturbance in cardiac output by an effect on the coronary microcirculation, but the evidence available would suggest that this would be a secondary phenomenon.

In the present study, by the time reinfusion of remaining reservoir blood was commenced after 2 h of hypotension, the stage of severe impairment of cellular function had been reached, so that although the term 'recovery' has been used because of literary acceptability, the final 2 h of the experiment is the period of established refractory shock. It is with this phase that the priority for further study lies.

The results obtained from the animals in which the classic Wiggers method was followed, i.e. replacement of absolute blood volume only, are very similar to Wiggers' own—low cardiac output and stroke volume, persistent increase in total peripheral resistance and continuing whole body hypoxia (Wiggers, 1942). Using the same experimental method, other workers have produced similar results, and have, like Wiggers, supported primary myocardial failure as the most important aetiological factor in irreversible shock (Lefer et al., 1967). Lefer and Martin have continued to demonstrate a myocardial depressant factor, believed by them to be elaborated by the ischaemic pancreas in severe shock states (Lefer and Martin, 1970). Ledingham and his colleagues have confirmed the presence of a myocardial depressing toxin, but have shown that, although it was demonstrated after 4 hours of haemorrhagic hypotension to 40 mmHg, it was not present after 2 h (Fisher et al., 1973). In the present study, refractory shock was well established before 2 h, at which time no depressant factor was likely to be elaborated. In addition, the concept of primary myocardial failure must be viewed critically in the light of the well-established clinical practice of aggressive volume replacement in shock resuscitation. For these reasons, the results obtained in the present study when perfusate was infused to restore functional normovolaemia as judged by a pos[illegible] central venous pressure of 0–2 mmHg must be [illegible]ed of critical importance.

Central venous pressure was [illegible] as the criterion of adequate volume infusion because of its wide use in clinical practice and because of the great variations in pulmonary artery pressures, both in individual experiments and in the series as a whole. However, the increase in cardiac output to 186 per cent of the resting value without elevation in venous pressure above the preselected value was believed to represent efficient cardiac function, at least in the short term. The parallel rise in stroke volume, and recorded pulse rates of resting or below resting figures, confirmed that the increased output was achieved inotropically. In this respect, it should be noted that the animals given no fluid additional to the reservoir blood at the time of reinfusion had a persistent tachycardia, with venous pressures below the recorded resting values. The sequence of events is believed to be as follows: provided that volume replacement is adequate, there is microcirculatory dilatation in response to peripheral hypoxia; the reduction in total peripheral resistance allows more ready increase in cardiac output, and, if venous return can be maintained, it seems likely that at least in the short term, cardiac output can be increased to above resting values, presumably in an attempt to satisfy tissue needs for oxygen. Quite clearly, the myocardium cannot continue to function thus indefinitely, and the reserve available will depend on age, pre-existing myocardial disease and the expected duration of the increased demands—hence Ledingham's critical time of 4 h in experimental conditions.

We have no data on left ventricle performance, because the standard methods available to assess this involve either a thoracotomy or indirect measurement of $LV\,\mathrm{d}p/\mathrm{d}t_{\max}$, which has been shown to be variable both at low and high flow states, especially when the use of catheter transducers inserted peripherally is involved. It is seldom that left and right ventricles fail independently in pathological states, and hence a normal central venous pressure was considered to imply satisfactory loadings.

It should also be noted that, even in those animals that remained in a low-output, vasoconstricted hypovolaemic state throughout the 4 h of study, the response to a 500-ml infusion of Dextran 70 was to increase cardiac output and stroke volume, with reduction in tachycardia and total peripheral resistance. This was achieved with no pathological elevation in central venous pressure. This would be consistent with the work of Hardy's group, who have transplanted the hearts of dogs in irreversible haemorrhagic shock to healthy recipients to sustain life for up to 1 week's observation (Hardy et al., 1975).

The relationship between cardiac output and tissue oxygen reserve has been established in unshocked dogs. Increased oxygen tensions following exposure to hyperbaric oxygenation to 3 atmospheres absolute in dogs subjected to total body washout to zero Hb was accompanied by normal cardiac output and 100 per cent survival when red cells were reinfused (Norman, 1975). In shocked animals, the use of steroids was followed by rapid restoration of a positive oxygen balance, and by near to resting values of cardiac output and total peripheral resistance (Smith and Norman, 1978). In the present series, however, the animals [illegible] alone remained in a low-output, vas[illegible]sted state, despite an increasing oxygen debt, presumably because of the loss of venous return.

While no conclusions could be drawn about reversible shock, or in [illegible] shock state (Wiggers and Ingraham, 1946), from [illegible]reported results, the gross discrepancy between irreversible shock and our refractory shock model could well be due to the differences in volume replacement. It should be noted however, that, despite adequate volume replacement, increased cardiac output and presumed satisfactory microcirculatory perfusion, the cumulative oxygen debt incurred in the hypotensive phase was not repaid in full after 2 h of normovolaemia. Although part of the reduced total peripheral resistance could be due to the lowered whole blood viscosity consequent on haemodilution to a haematocrit of 67 per cent of the resting value (Sunder-Plassmann et al., 1972), the majority was considered to be due to persistent peripheral dilatation caused by local hypoxia and acidosis. There can be no doubt that myocardial failure is likely to occur if output remains at such high values, but peripheral vasomotor collapse rather than primary myocardial failure is suggested as a more likely causative factor in refractory shock.

The absence of any difference in the figures for arterial lactate is strange, but the variation in individual results was wide, and in the group given additional fluid, the washout of lactate was likely to contribute to the levels remaining high despite improvement in oxygen consumption (Bergentz et al., 1969).

Conclusions

The primary problem in refractory shock is microcirculatory motor collapse, secondary to prolonged tissue hypoxia and the consequences of it. Provided venous return is maintained, there is no evidence of primary myocardial failure, although it is suggested that this may occur as a later feature caused by high output failure combined with the effect of hypoxia and acidosis on the coronary circulation.

Volume replacement alone is not considered adequate resuscitation in refractory shock, as evidenced by above-resting values for cardiac output and stroke volume and by a persistent total oxygen debt.

References

APPELGREN K. L. and LEWIS D. H. (1970) Capillary [illegible] and capillary transport in dog skeletal muscle afte[illegible] RBC aggregation and disaggregation. *Eur. Sur* [illegible] 161–170.

BAUE A. E. (1968) Recent developments in the stud[illegible] ment of shock. *Surg. Obstet. Gynecol.* **127**, 84[illegible]

BERGENTZ S. E., CARLSTEN A., GELIN L. E. et al. ([illegible] acidosis in experimental shock. *Ann. Surg.* [illegible] 23[illegible]

BRAND E. D. and LEFER A. M. (1966) Myocardial dep[illegible] in plasma from cats in irreversible post-ol[illegible] *Proc. Soc. Exp. Biol. Med.* **122**, 200–203.

FISHER W. D., HEIMBACH D. W., MCARDLE C. S. [illegible] al. ([illegible]3) [illegible] circulating depressant effect following [illegible] haemorrhagic shock. *Br. J. Surg.* **60**, 392–394.

HARDY J. D., KONDO Y., TURNER M. D. et al. ([illegible]) A success[illegible] orthotopic allotransplantation of hearts [illegible] irreversib[illegible] shocked dogs. *Surgery* **77**, 126.

HARKINS H. H. (1941) Recent advances in the study and manag[illegible]ment of traumatic shock. *Surgery* **9**, 231–294, 447–48[illegible], 607–655.

HUNT A. C. (ed.) (1972) *Pathology of Injury: Current Knowledge and Future Development.* Report of a Working Party of the Royal College of Pathologists. London, Harvey Miller & Metcalf, pp. 53–64.

LEFER A. M., COWGILL R., MARSHALL F. F. et al. (1967) Characterisation of a myocardial depressant factor present in haemorrhagic shock. *Am. J. Physiol.* **213**, 492–498.

LEFER A. M. and MARTIN J. (1970) Origin of myocardial depressant factor in shock. *Am. J. Physiol.* **218**, 1423–1427.

LONGERBEAM J. K., LILLEHEI, R. C. and SCOTT W. R. (1962) The nature of irreversible shock. A hemodynamic study. *Surg. Forum* **13**, 1–3.

NORMAN J. N. (1975) Haemodynamic studies in total blood replacement. *Bibl. Haematol.* **41**, 203–208.

SMITH J. A. R. and NORMAN J. N. (1978) The use of glucocorticoids in refractory shock. *Surg. Gynecol. Obstet.* **147** (In the press.)

STALKER A. L. (1970) The microcirculation in shock. *Clin. Pathol.* **23**, 10–15.

SUNDER-PLASSMANN L., KLOVERKORN W. P. and MESSMER K. (1972) Hemodynamic and rheological changes induced by hemodilution with colloids. In MESSMER K. and SCHMIDT-SCHONBEIN H. (ed.) *Hemodilution: Theoretical Basis and Clinical Application.* Basle, Karger.

WIGGERS C. J. (1942) The present status of the shock problem. *Physiol. Rev.* **22**, 74–123.

WIGGERS H. C. and INGRAHAM R. C. (1946) Hemorrhagic shock: definition and criteria for its diagnosis. *J. Clin. Invest.* **25**, 30–36.

WIGGERS H. C., INGRAHAM R. C., ROEMHILD F. et al. (1948) Vasoconstriction and the development of irreversible hemorrhagic shock. *Am. J. Physiol.* **153**, 511–522.

Paper accepted 26 June 1978.

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Sequential patterns of haemodynamic and metal changes in experimental hypovolaemic shock.
I. Responses to acute haemorrhage

J. PARDY AND H. A. F. DUDLEY*

SUMMARY

Little is known about cardiorespiratory changes during the development of hypovolaemia. This study attempts to provide such information and compares the period of bleeding with that of established hypovolaemia.

Eleven anaesthetized and ventilated greyhounds were bled and analyses of cardiopulmonary function made at fixed intervals both during and after haemorrhage. Six sequential patterns of cardiopulmonary and metabolic change were recognized. It was apparent that bleeding caused the first three phases of change, recovery from the effects of bleeding the next two and steady hypovolaemia the last. The event of bleeding is the main factor that elevates total peripheral resistance and reduces tissue perfusion with consequent lowering of oxygen consumption and alkalosis secondary to impaired carbon dioxide production; when bleeding ceases these changes partially reverse in a manner characteristic of that induced by the reinfusion of shed blood; and hypovolaemia per se has a relatively weak influence.

These findings provide an explanation for disparities in previous published reports and have obvious clinical implications.

DETAILED studies of the cardiorespiratory changes associated with hypovolaemia have resulted in widely disparate findings concerning the behaviour of certain indices. For example, total peripheral resistance in man has been reported to be invariably raised (Hopkins et al., 1965; Wilson et al., 1965), generally raised, but with considerable variation in that it is sometimes normal or below normal (Cournand et al., 1943; Monson and Shoemaker, 1968), normal (Rossoff et al., 1965) or low (Shoemaker et al., 1966). Similarly, in the hypovolaemic dog, total peripheral resistance has been described as markedly increased (Reynell et al., 1955; Cook and Webb, 1968), slightly or moderately increased (Wiggers, 1950) or 'questionably reduced' (Fowler and Franch, 1957).

Disparities such as those described remain unexplained, possibly because studies of hypovolaemia have been confined almost entirely to the period of established shock and little is known concerning the effects of bleeding. We studied the development of hypovolaemia with the hypothesis that the variation in results might be explained by sequential processes which had been studied at different times.

Materials and methods

Eleven greyhounds with a mean weight of 24 kg were used. Anaesthesia was induced with thiopentone sodium 20 mg/kg i.v. followed immediately by pentobarbitone sodium 6 mg/kg. The animal was then placed supine and remained so throughout the study. A cuffed endotracheal tube was inserted and ventilation with room air maintained by a volume-cycled pump respirator. A thermocouple probe was placed in the mid-oesophagus for the recording of core temperature, and

relaxant anaesthesia was maintained wit
i.v. infusion of pancuronium bromide (Pavul
methohexitone sodium (Brietal Sodium, Eli
were passed into the pulmonary artery for p
and sampling of mixed venous blood, into a
pressure recording, into a carotid artery for sa
blood and for bleeding and into the right atr
ment of central venous pressure. Pressures
with strain gauges (SE Laboratories SEM
preamplified (SAN-EI Biophysiograph 180) a
traced on a multichannel potentiometric reco
Watanabe).

Cardiac output was measured by the dire
For the latter, expired air was directed by a c
1969) through an online analysing system
mixing bags, a paramagnetic oxygen analyser
OA.272), an infrared carbon dioxide analyse
graph, Type BE) and a dry spirometer (
CD4). Arterial and mixed venous blood sam
for pH, $P\mathrm{o}_2$ and $P\mathrm{co}_2$ using a microelectro
Micro System, Type BMS3, Radiometer). T
concentrations of gases used to calibrate the
and the carbon dioxide electrode had been
Haldane method. In practice, expired air g
were read before and after sampling of a
venous blood, and the mean values employe
Arterial blood haemoglobin concentration
Coulter Counter, Model S.

All calculations were performed on a
computer. A blood-gas factor of 4 per ce
readings obtained with the oxygen electrod
1967), and blood pH, $P\mathrm{co}_2$ and $P\mathrm{o}_2$ were corr
ture (Kelman and Nunn, 1966). The perc
with oxygen was derived from the tension
for dog blood (Rossing and Cain, 1966). Ox
determined on the basis that the oxygen-co
haemoglobin was 1·39 ml/g (Sykes et al., 1
solubility factor for oxygen was 0 003 ml/mm
put was calculated from the Fick formula,
tion being derived from the inspired and expi
tions. Physiological dead space was deter
Enghöff modification (Enghöff, 1938) of th
and total venous admixture was calculated f
mixing equation.

$$\dot{Q}_{\mathrm{s}}/\dot{Q}_{\mathrm{t}}=(C'_{\mathrm{c}}-C_{\mathrm{a}})/(C'_{\mathrm{c}}-C$$

where C_{a} is the arterial oxygen content an
venous oxygen content. End-pulmonary
content (C'_{c}) was calculated by assuming
end-pulmonary capillary oxygen tensions we
oxygen tension was calculated from the alve
using gas tensions. Expired air volumes and g
were corrected for temperature and pressure.

Vascular resistance indices were deter
equation

$$\mathrm{RI}=13{\cdot}33\ (\text{perfusion pressure})\ \mathrm{kg}$$

where RI is the vascular resistance index
and CO is cardiac output in ml/min. The p
for pulmonary vascular resistance was mean
pressure minus pulmonary artery wedge

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London.

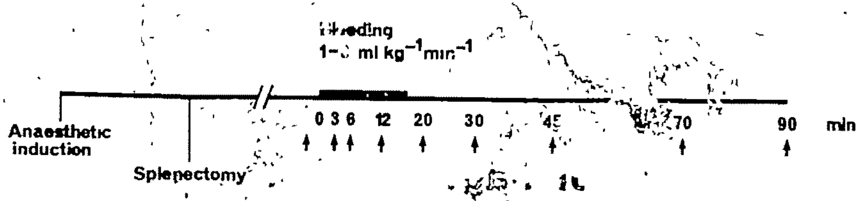


Fig. 1. Plan of the experiment. Measurements were taken at points indicated by arrows.

total peripheral resistance was mean systemic arterial pressure minus central venous pressure.

Base excess was determined from arterial pH, $P\mathrm{co}_2$ and haemoglobin values using an alignment nomogram (Siggaard-Andersen, (1963). The Walsh non-parametric test for related samples was employed for inferential statistics (Siegel, 1956).

Fig. 1 shows the plan of the experiment. After insertion of the cannulas the spleen was removed to obviate the effects of the splenic reservoir of blood, and tidal volume was adjusted so that end-tidal carbon dioxide concentration was approximately 4·5 per cent. The tidal volume setting remained unchanged throughout the experiment. After a period of stabilization baseline measurements were made. Blood was then pumped (Watson-Marlow HR Flow Inducer) from the carotid artery cannula at a constant rate of between 1 and 3 ml kg^{-1} min^{-1} until the systemic arterial pressure began to fall sharply. Shed blood was collected in airless plastic bags containing acid–citrate–dextrose solution (NIH Solution A; Mollison, 1972). After cessation of rapid bleeding, systemic arterial pressure was maintained at approximately 85 mmHg by the removal of further blood or the reinfusion of shed blood via a peripheral vein, until the experiment was terminated 90 min from the start of bleeding. Measurements were made at the times shown in *Fig.* 1.

Results

All dogs but one survived the 90 min of hypovolaemia, the death occurring 80 min after the onset of bleeding (results from this animal acquired during the first 30 min only have been used). Absolute values of indices before bleeding are given in *Table I.* On the basis of qualitative changes in systemic arterial pressure, cardiac output and total peripheral resistance, six sequential patterns of response to haemorrhage could be distinguished (*Table II*). The cardiorespiratory data were assembled as described below for analysis of changes during each phase and the results are shown in *Table III.*

Results are reported as mean ± s.d., and percentage values for indices other than total venous admixture and physiological dead space ratio are of the control value. Because measurements were made intermittently the actual duration of each phase is not known, and the changes reported have only qualitative value except in relation to each other.

Phase I

To enable statistical analysis, the changes in the various indices during the period from the start of bleeding to the arbitrarily chosen point at which systemic arterial pressure had declined by approximately 5 per cent of the pre-bleed level were determined. A number of the values for indices at this point were derived by interpolation. Systemic arterial pressure fell at a rate of 0·6 per cent per minute, cardiac output and pulmonary artery pressure fell by similar proportions, and total peripheral resistance and pulmonary vascular resistance rose. Oxygen consumption, carbon dioxide production and $P\mathrm{aco}_2$ decreased, arterial pH rose and total venous admixture and physiological dead space ratio (physiological dead space/tidal volume) did not change.

Table I: ABSOLUTE VALUES BEFORE BLEEDING (mean ± s.d.)

Mean systemic arterial pressure (mmHg)	168±12
Cardiac output (ml min^{-1} kg^{-1})	183±43
Total peripheral resistance index (dyn s kg cm^{-5})	775±209
Mean pulmonary artery pressure (mmHg)	19±7
Pulmonary vascular resistance index (dyn s kg cm^{-5})	47±15
Oxygen consumption (ml kg^{-1} min^{-1})	8·0±1·3
Carbon dioxide production (ml kg^{-1} min^{-1})	6·5±1·1
pH arterial blood	7·41±0·02
$P\mathrm{co}_2$ arterial blood (mmHg)	39±2
Base excess (mmol/l)	0·5±1·4
Total venous admixture (%)	11±5
Physiological dead space ratio (%)	53±5

Table II: QUALITATIVE CHANGES IN CARDIAC OUTPUT, TOTAL PERIPHERAL RESISTANCE AND SYSTEMIC ARTERY PRESSURE DETERMINING THE SIX PHASES

I: Initial bleeding	CO falls, TPR rises, SAP well maintained
II: Further bleeding	CO falls, insufficient rise in TPR to maintain SAP
III: Late bleeding	CO falls, no change in TPR, SAP falls sharply
IV: Immediately after bleeding	CO unchanged, TPR falls, further fall in SAP
V: Subsequently after bleeding	CO rises, no change in TPR, SAP rises
VI: Steady hypovolaemia	No change in CO, TPR or SAP

CO, Cardiac output; TPR, total peripheral resistance; SAP, systemic arterial pressure.

Phase II

All results reported in this and subsequent phases were derived directly. Because the timing of measurements was fixed while the timing of cardiopulmonary responses varied, data from consecutive measurements could not be correlated with the phases in all animals. During this phase systemic arterial pressure fell from approximately 95 to 75 per cent of the control value at a rate of 3·4 per cent per minute. Changes in all other indices were similar to those observed during phase I.

Phase III

As bleeding continued systemic arterial pressure began to decline rapidly and the removal of blood was slowed or stopped. Systemic arterial pressure fell at a rate of 5·1 per cent per minute, the result of a decline in cardiac output without any increase in total peripheral resistance. The decline in oxygen consumption and carbon dioxide production was greater than

Table III: CHANGES DURING THE S[illegible]

	I (*n* = 11)	[illegible]	[illegible]	[illegible]	V (*n* = 11)	VI (*n* = 10)	
Time after onset of bleeding (min)	0–8	[illegible]	[illegible]	[illegible]	32–47	53–90	
Volume of blood shed (ml kg⁻¹)	15±8	[illegible]		[illegible]			
Mean systemic arterial pressure (%)	−5±2*	−17±12†	[illegible]	[illegible]	11±11*	7±10§	
		96±3†	[illegible]	[illegible]	36±8*	[illegible]	53±11*
Cardiac output (%)	−32±14*	[illegible]	−24±10*	[illegible]	8±6*	[illegible]	
	100	70±17†	54±14*	[illegible]	26±8*	33±9*	31±9*
Total peripheral resistance (%)	45±36*	73±52†	−8±56§	−76±76*	−6±63§	39±49§	
	100	149±43†	173±41*	220±106*	160±63*	155±39*	194±71*
Mean pulmonary artery pressure (%)	−33±12*	−19±10†	−26±11*	8±13§	9±14†	5±9§	
	100	66±11†	56±15*	29±8*	34±12*	43±17*	48±17*
Pulmonary vascular resistance (%)	47±15*	56±36†	39±44‡	23±66§	−37±76§	81±147‡	
	100	156±73	149±33*	244±104*	278±156*	262±109*	343±174*
Oxygen consumption (%)	−8±5*	−9±6†	−17±9*	6±9§	15±22*	1±10§	
	100	90±5†	88±7*	70±10*	74±10*	87±10*	87±12*
Carbon dioxide production (%)	−9±7*	−11±4†	−15±5*	5±6§	10±18‡	6±7§	
	100	91±9†	87±8*	70±5*	73±8*	83±18*	90±18§
pH arterial blood	0·01±0·01*	0·01±0·01§	0·01±0·02§	−0·04±0·05*	−0·03±0·05§	−0·02±0·06§	
	7·41±0·02	7 41±0·03§	7·43±0·03†	7·43±0 04*	7·37±0·07§	7·34±0·11*	7·32±0·06*
P_{CO_2} arterial blood (mmHg)	−2±2*	−2±2‡	−3±2‡	3±3†	3±5*	2±4§	
	39±2	38±3§	36±4†	33±4*	36±3*	39±6§	42±4§
Base excess (mmol/l)	−0·2±0 8§	−0·3±0·7§	−1·1±2·0†	−1·9±2·6‡	−0·4±1·7§	−0·6±2·5§	
	0·5±1·4	−0·2±1·8§	−0·1±1·9§	−1·2±1·9*	−3·7±4 2*	−4·3±3·3*	−4 8±3·3*
Total venous admixture (%)	0±3	−2±2§	−2±2†	1±2§	1±2§	1±3§	
	11±5	9±6§	9±3§	6±3‡	6±4‡	7±5§	7±6§
Physiological dead space ratio (%)	1±4§	2±2§	4±2†	1±4§	−1±4§	0±2§	
	53±5	56±3§	57±4§	60±3*	61±4*	60±5*	60±6*

All values are mean ±s.d. Percentage values (except for total venous admixture and physiological dead space ratio) are of control level.
The first figure is the change during the phase, the second figure is the value at the start of the phase and significance testing is with the control value.
* $P<0·01$; † $P<0·02$; ‡ $P<0·03$; § not significant.

in previous phases, total venous admixture fell and the physiological dead space ratio increased. Arterial pH was elevated despite a decline in base excess.

Phase IV

After cessation of bleeding a sharp fall in total peripheral resistance unaccompanied by any change in cardiac output resulted in a continued decline in systemic arterial pressure. There was no further reduction in oxygen consumption or carbon dioxide production and Pa_{CO_2} rose for the first time. Arterial pH, significantly elevated above control level, fell sharply with the rise in Pa_{CO_2} and a further fall in base excess.

Phase V

Cardiac output and systemic arterial pressure both rose while total peripheral resistance remained unchanged. Oxygen consumption and carbon dioxide production now increased.

Phase VI

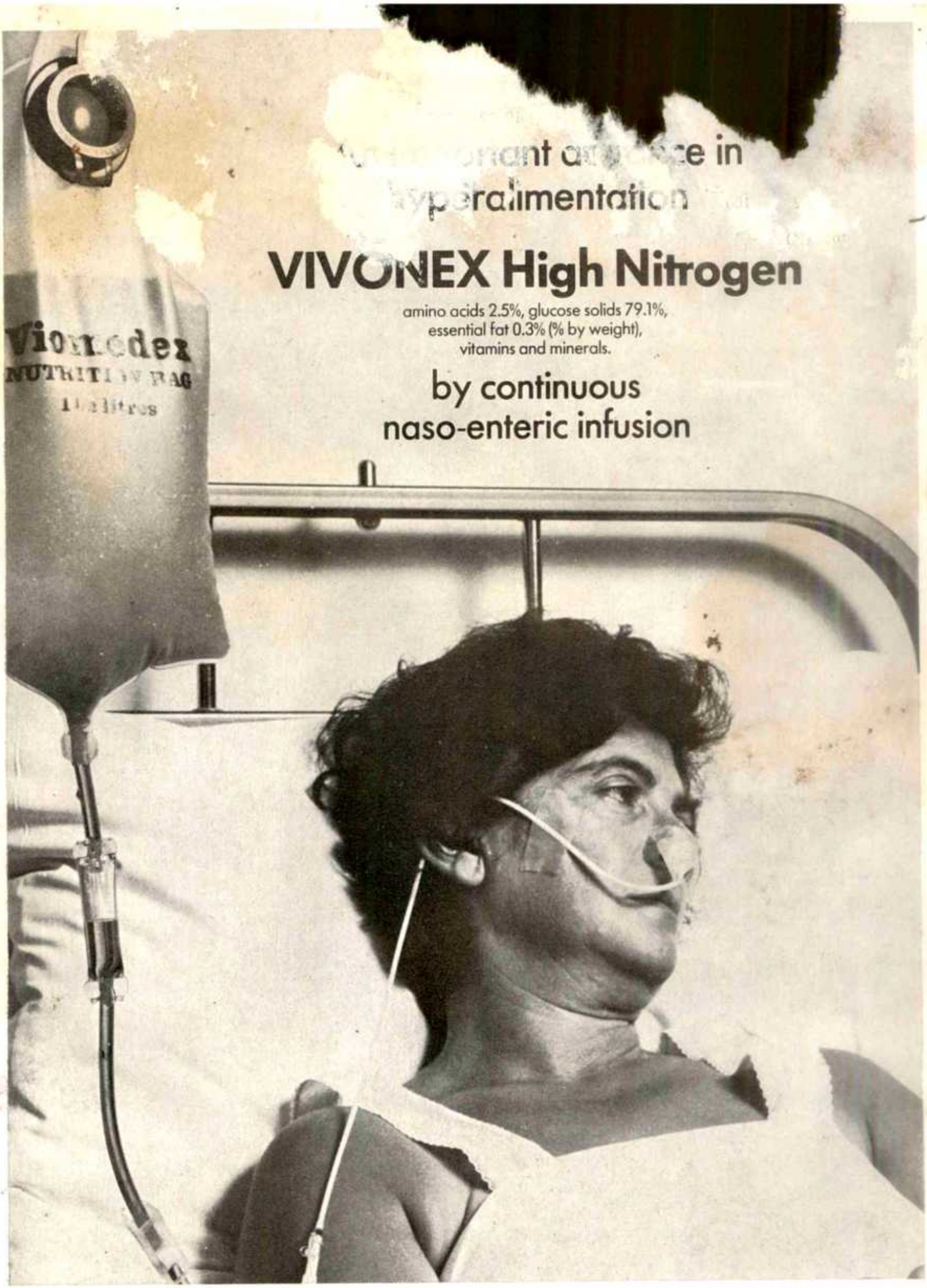
During this period of steady hypovolaemia there was no significant change in any index except pulmonary vascular resistance, which increased.

Discussion

The reports of early workers that cardiac output is reduced when blood volume is depleted have not since been disputed. By contrast, there has been a conspicuous lack of unanimity about changes in certain other indices during haemorrhagic shock and to add to the confusion many of the reported changes have been of doubtful or no significance. Suggestions that widely differing findings may be related to the dynamic nature of shock (Walters, 1972) and to the duration and depth of shock (Shoemaker et al., 1967) carry the implication that there are patterns of change in shock and that results will vary according to the stage at which measurements are made. However, those patterns of change which have been described (Kim et al., 1969; Bassin et al., 1971; Vladek et al., 1971) have not explained the disparities between published results.

Three distinctive features of the current study were the rapid measurement of cardiac output by the Fick method made possible by the online system, use of a fixed tidal volume and the performance of analyses during continuous bleeding. These techniques enabled the recognition of six sequential patterns of change hitherto not described. It is important, however, that the limitations of analysis of data acquired by intermittent measurement of a continuously changing process be recognized, especially when the time course is variable. A consequence of the latter was that not all the phases were identified in all the animals, phase II being observed in 7 dogs and phase III in 8. With these considerations in mind, it is clear that the existence of the six phases described can only be inferential.

The cause-and-effect relationships during the phases can be surmised by examination of the data in *Table III*. It will be seen that a number of indices underwent three sequential changes coinciding with



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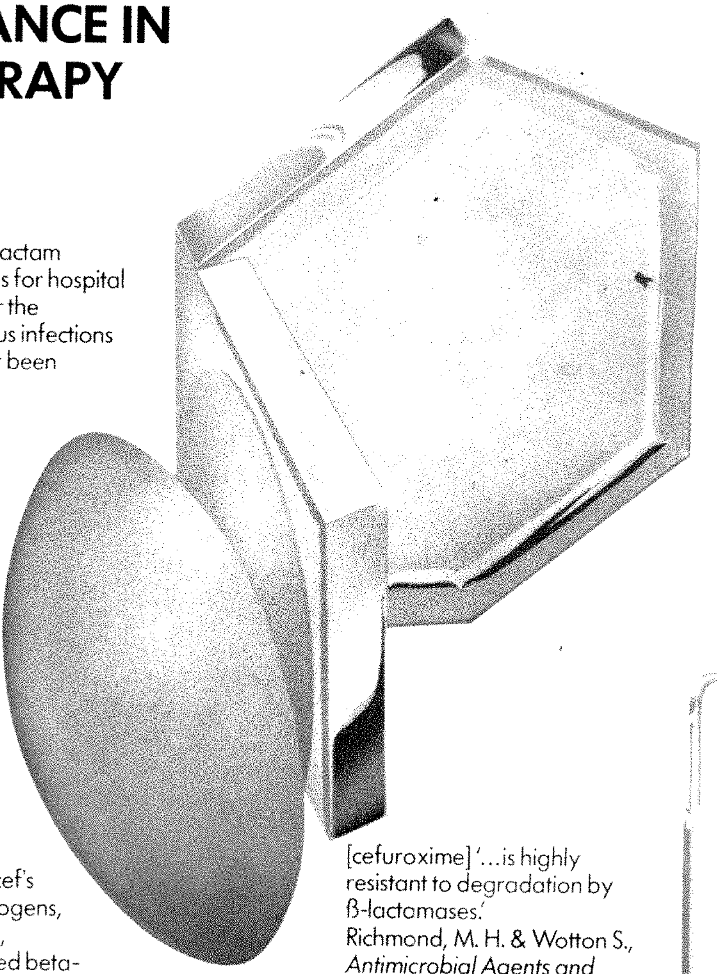

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Greatly enhanced stability to beta-lactamases

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The ability to resist destruction results in a greatly extended clinical spectrum. Zinacef's bactericidal effect extends to many pathogens, both Gram-positive and Gram-negative, resistant or partially resistant to established beta-lactam antibiotics.

[cefuroxime] '...is highly resistant to degradation by ß-lactamases.'
Richmond, M. H. & Wotton S., *Antimicrobial Agents and Chemotherapy* (1976) **10,** 219

With important therapeutic properties

- Zinacef has high bactericidal activity.
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- Zinacef has minimal toxicity, giving a wide margin of safety.
- Clinical trials have shown excellent renal tolerance.
- Zinacef can safely be used in neonates.
- Patient tolerance is excellent both intramuscularly and intravenously.
- Zinacef is compatible with commonly-used intravenous infusion fluids.
- There are no known clinically relevant adverse drug interactions.
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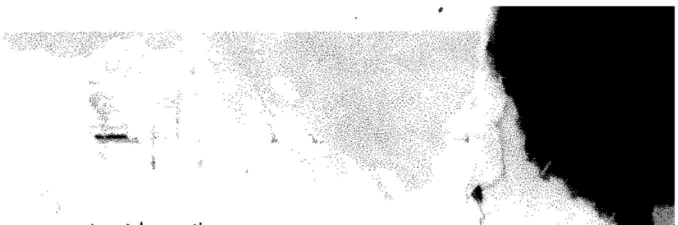

> …this wide antib[illegible] te[illegible] [Zinacef] a usefu[illegible] infections requiring promp[illegible] [illegible] apy before the causative pathogen has been identified.'
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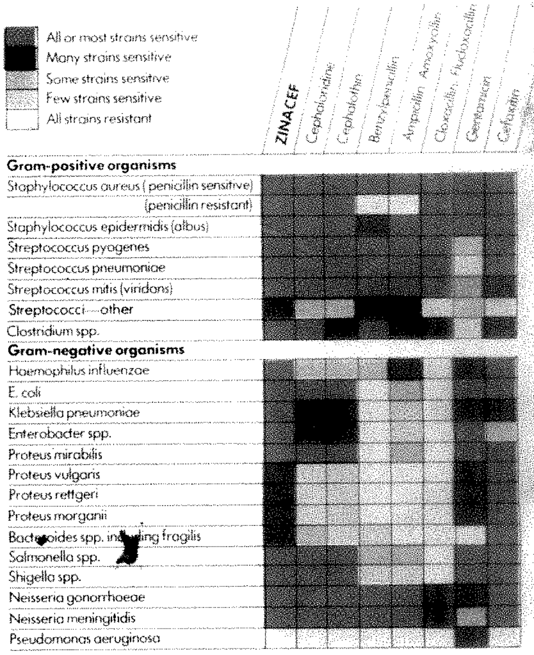
> *British Medical Journal* (1978) **1**, 1279



▓ All or most strains sensitive
■ Many strains sensitive
▒ Some strains sensitive
░ Few strains sensitive
□ All strains resistant

	ZINACEF	Cephaloridine	Cephalothin	Benzylpenicillin	Ampicillin Amoxycillin	Cloxacillin Flucloxacillin	Gentamicin	Cefoxitin
Gram-positive organisms								
Staphylococcus aureus (penicillin sensitive)	▓	▓	▓	▓	▓	▓	▓	▓
(penicillin resistant)	▓	▓	▓	□	□	▓	▓	▓
Staphylococcus epidermidis (albus)	▓	▓	▓	■	▓	▓	▓	▓
Streptococcus pyogenes	▓	▓	▓	▓	▓	▓	▒	▓
Streptococcus pneumoniae	▓	▓	▓	▓	▓	▓	░	▓
Streptococcus mitis (viridans)	▓	▓	▓	▓	▓	▓	▒	▓
Streptococci—other	■	▒	▒	■	■	▒	░	▒
Clostridium spp.	▓	▓	■	▓	■	■	░	▓
Gram-negative organisms								
Haemophilus influenzae	▓	░	░	░	■	░	▓	▓
E. coli	▓	▓	▓	░	▒	░	▓	▓
Klebsiella pneumoniae	▓	■	■	░	░	░	■	■
Enterobacter spp.	▓	■	■	░	░	░	▓	▒
Proteus mirabilis	▓	▓	▓	░	▒	░	▓	▓
Proteus vulgaris	■	░	░	░	░	░	■	▓
Proteus rettgeri	■	░	░	░	░	░	■	▓
Proteus morganii	■	░	░	░	░	░	■	▓
Bacteroides spp. including fragilis	■	░	░	░	░	░	░	▓
Salmonella spp.	▓	▓	▓	▒	▒	░	▓	▓
Shigella spp.	▓	▓	▓	░	▒	░	▓	▓
Neisseria gonorrhoeae	▓	▓	▓	▓	▓	■	■	▓
Neisseria meningitidis	▓	▓	▓	▓	▓	■	▒	▓
Pseudomonas aeruginosa	□	□	□	□	□	□	■	□

ZINACEF

Prescribing information

Presentation
Vials of 250mg, 750mg and 1·5 gram and infusion pack of 1·5 gram. All containing cefuroxime as cefuroxime sodium.

Indications
Serious bacterial infection, especially where the organisms have not yet been identified.
Conditions include:
Chest infections
Septicaemia
Soft tissue infections
Obstetric and gynaecological infections
Bone and joint infections
Urinary tract infections
Ear, nose and throat infections
Meningitis
Gonorrhoea

Dosage
Adults: Generally 750mg t.d.s. i.m. or i.v. Severe infections 1·5 gram t.d.s. i.v. Frequency of injections can be increased to six-hourly if necessary.
Infants and children: 30 to 100mg/kg/day in three or four divided doses. 60mg/kg/day will be appropriate for most infections.
Neonates: 30 to 100mg/kg/day in two or three divided doses.
Gonorrhoea: Single dose of 1·5 gram (2 x 750mg i.m. into different sites).

Contra-indications
Hypersensitivity to cephalosporins.

Precautions
Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins.
As with all drugs, Zinacef should be administered with caution during the early months of pregnancy.
Zinacef does not interfere with enzyme-based tests for glycosuria.
Cephalosporins interfere with tests for glycosuria which use copper reduction or ferricyanide methods and with the alkaline picrate assay for creatinine.
As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms.
Zinacef should not be mixed in the syringe with aminoglycoside antibiotics.
Reduce dosage when renal function is markedly impaired.
Cephalosporins at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as frusemide, as these combinations are suspected of adversely affecting renal function. Clinical experience with Zinacef has shown that this is not likely to be a problem at the recommended dose levels.

Side effects
Adverse reactions are rare and generally mild and transient, e.g., rashes, gastro-intestinal disturbance, candida intertrigo, decreased haemoglobin concentration, eosinophilia, a positive Coombs' test, transient rises in serum liver enzymes and transient pain (after i.m. injection).

Storage
The powder in the infusion pack and vials should be stored below 25°C and protected from light.

Product Licence number
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Price to Hospital (exclusive of VAT)

	£	
5 x 250mg	0·70	per vial
5 x 750mg	2·10	per vial
1·5 gram	4·20	

Glaxo

Full prescribing information on Zinacef (trade mark) is available from
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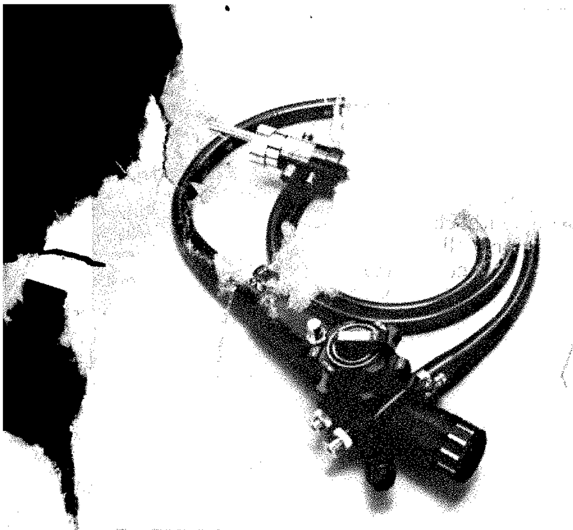

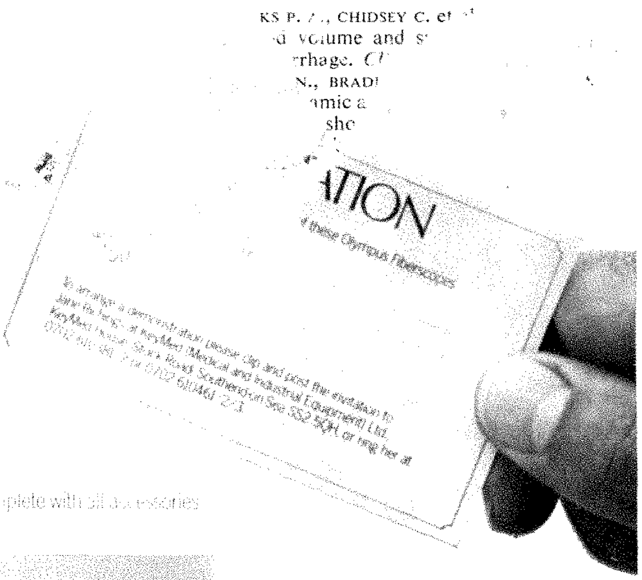

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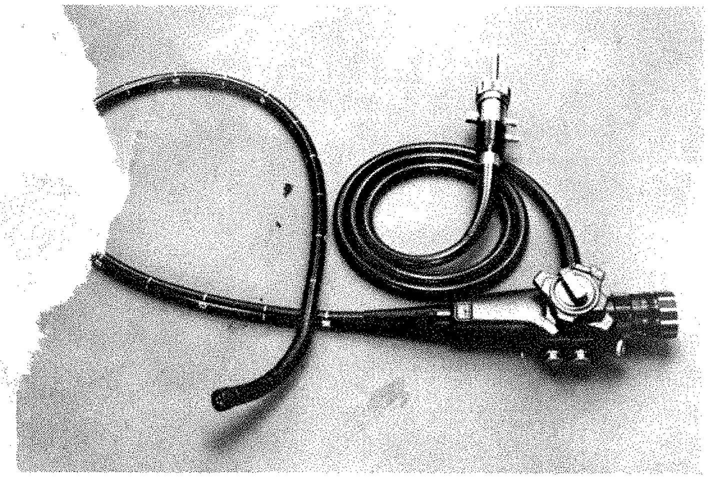

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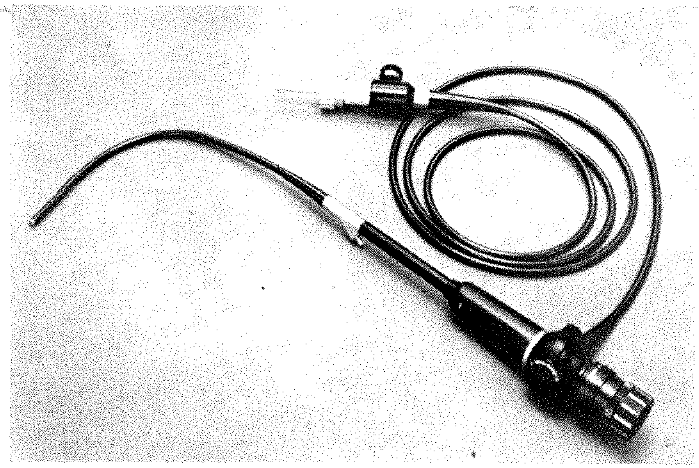

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Circ. Res. **5**, 153–156.

PKINS R. W., SABOA G., PENN L. et al.
aspects of hemorrhagic and sept
127–131.

ELMAN G. R. and NUNN J. E. (1966) Nomograms for co of blood Po_2, Pco_2, pH and base excess for time and temperature. *J. Appl. Physiol.* **21**, 1484–1490.

KHO L. K. and SHOEMAKER W. C. (1967) Cardiorespiratory changes in acute hemorrhage. *Surg. Gynecol. Obstet.* **124**, 826–832.

KIM S. I., DESAI J. M. and SHOEMAKER W. C. (1969) Sequence of cardiorespiratory alterations after gradual prolonged hemorrhage in conscious dogs. *Am. J. Physiol.* **216**, 1044–1050.

MOLLISON P. L. (1972) *Blood Transfusion in Clinical Medicine*, 5th ed. Oxford, Blackwell Scientific, p. 686.

MONSON D. O. and SHOEMAKER W. C. (1968) Sequence of hemodynamic events after various types of hemorrhage. *Surgery* **63**, 738–749.

NAIMARK A., DUGARD A. and RANGNO R. E. (1968) Regional pulmonary blood flow and gas exchange in hemorrhagic shock. *J. Appl. Physiol.* **25**, 301–309.

PARDY B. J. and DUDLEY H. A. F. (1977a) Comparison of pulmonary artery pressures and mixed venous oxygen tension with other indices in acute haemorrhage: an experimental study. *Br. J. Surg.* **64**, 1–5.

PARDY B. J. and DUDLEY H. A. F. (1977b) Post-traumatic pulmonary insufficiency. *Surg. Gynecol. Obstet.* **144**, 259–269.

PARDY B. J. and DUDLEY H. A. F. (1979) Sequential patterns of haemodynamic and metabolic changes in experimental hypovolaemic shock. II. Responses to reinfusion of shed blood. *Br. J. Surg.* **66**, 89–92.

R. F. (196) Neural factors regulating [illegible]
ILLS L. C. and MOYER J. H. (ed.) *Shock and Hypotension.*
Grune & Stratton, pp. 22–31.

ER W. C., CAREY J. S., MOHR P. A. et al. (1966) Hemo-
amic measurements in various types of clinical shock.
h. Surg. **93**, 189–195.

SHOE ER W. C., PRINTEN J., AMATO J J. et al. (1967) Hemodynamic patterns after acute anesthetized and unanesthetized trauma. *Arch. Surg.* **95**, 492–499.

SIEGEL S. (1956) *Nonparametric Statistics for the Behavioural Sciences*, International Student Edition. Japan, McGraw-Hill/Kogakusha, pp. 83–87.

SIGGAARD-ANDERSEN O. (1963) Blood acid-base alignment nomogram. Scales for pH, Pco_2, base excess of whole blood of different hemoglobin concentrations, plasma bicarbonate and plasma total CO_2. *Scand. J. Clin. Lab. Invest.* **15**, 211–217.

SYKES M. K. (1969) A pressure-operated collect valve for respiratory studies during intermittent positive pressure ventilation. *Br. J. Anaesth.* **41**, 189–190.

SYKES M. K., ADAMS A. P., FINLAY W. E. I. et al. (1970) The cardiorespiratory effects of haemorrhage and overtransfusion in dogs. *Br. J. Anaesth.* **42**, 573–584.

VLADEK B. C., BASSIN R., KARK A. E. et al. (1971) Rapid and slow hemorrhage in man: II. Sequential acid-base and oxygen transport responses. *Ann. Surg.* **173**, 331–336.

WALTERS G. (1972) Haemodynamics—General. In. LEDINGHAM I. MCA. and MCALLISTER T. A. (ed). *Conference on 'Shock'*. London, Kimpton, pp. 3–8.

WIGGERS C. J. (1950) *Physiology of Shock.* New York, Commonwealth Fund, p. 223.

WILSON R. F., THAL A. P., KINDLING P. H. (1965) Hemodynamic measurements in septic shock. *Arch. Surg.* **91**, 121–129.

Paper accepted 3 August 1978.

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interpretation of the likely sequence of events wh occurred as a result of bleeding.

Bleeding period

The reduction of venous return with bleeding caus a progressive fall in cardiac output, but the initial rise in total peripheral resistance was sufficient to maintain systemic arterial pressure. Though perfusion pressure was maintained, effective tissue blood flow was impaired, as shown by the reduction of oxygen consumption and carbon dioxide production. This reduction in carbon dioxide production was responsible not only for the fall in Pa_{CO_2}, ventilation being constant, but also for the rise in arterial pH, there being no increase in base excess. With further bleeding, total peripheral resistance increased at a slower rate and systemic arterial pressure was less effectively maintained. Total venous admixture was reduced, probably because the effects of ventilation/perfusion inequalities were lessened and blood flow through anatomical shunts was reduced (Sykes et al., 1970). Physiological dead space increased because a greater proportion of alveoli were not perfused.

Early period after bleeding

Recovery from the effects of bleeding was associated with a sharp fall in total peripheral resistance which is hard to explain. The conventional mechanisms responsible for increasing total peripheral resistance during hypovolaemia are reduced baroreceptor activity consequent upon less stretch and increased chemoreceptor activity secondary to accumulation of metabolites in the glomus tissue. These mechanisms cannot have been reversed when bleeding ceased, however, for there was no increase in systemic arterial pressure (which fell) and almost certainly no increase in perfusion of glomus tissue because cardiac output was unchanged. The phenomenon, also observed in relation to heart rate (Rushmer, 1965), remains unexplained.

Arterial pH, previously elevated despite a reduced base excess, fell sharply at this time because of the combined effects of a rise in Pa_{CO_2} and a further fall in base excess.

Subsequent (phase V) changes during this period included a rise in cardiac output and an improvement in tissue perfusion as evidenced by the changes in oxygen consumption and carbon dioxide production. These changes were remarkably similar to those resulting from the initial reinfusion of shed blood as described in the accompanying paper (Pardy and Dudley, 1979).

Late period after bleeding

Contrasting with the dynamic states during the period of bleeding and immediately after, the 37 min of phase VI were relatively static and the only significant change was a large increase in pulmonary vascular

to be ing cea and (c) hypovolaemia y weak influence on these indices. these conclusions, it is likely that ing during established hypo- with h cause total peripheral resistance to rise and oxygen consumption to fall and that th changes will partially reverse when bleeding stops.

The above concepts provide some explanation the disparities mentioned at the beginning of paper. When measurements have been made incremental bleeds (Kim et al., 1969), the finding reflect the effects of recovery from the prec bleed. When a reservoir system has been empl the results will be affected by whether blood is e or leaving the experimental subject at the t measurement. And in clinical studies, the matc of data to determine patterns of change will hindered by the fact that bleeding may be occurring unbeknown to the investigator.

The data from this study contradict the suggestion that systemic arterial pressure is well maintained during bleeding until total peripheral resistance falls (Kho and Shoemaker, 1967), and do not support the concept that the increase in physiological dead space during hypovolaemia is related to reduced pulmonary artery pressure (Askrog, 1966; Naimark et al., 1968). We suggest that reduced physiological dead space may be related more closely to the reduction of pulmonary blood volume than of pulmonary artery pressure. Finally, comment should be made on the close correlation between changes in pulmonary artery pressure and cardiac output during bleeding (Pardy and Dudley, 1977a). This relationship was not maintained later in shock when pulmonary artery pressure rose more than cardiac output, the result of a greater increase in pulmonary vascular resistance than of total peripheral resistance (pulmonary artery wedge pressure did not change).

The finding that the most marked derangements occur during bleeding has clinical relevance. Bleeding in surgical patients is frequently difficult to detect, and appropriate measurement made on suspicion may be of more value than conventional measurements which tend to recognize only the effects of severe blood loss. Measurements which are practicable include pulmonary artery pressure and end-tidal carbon dioxide concentration.

Acknowledgement

We are grateful for a grant from the Wellcome Trust which helped support this work.

References

ADAMS A. P., MORGAN-HUGHES J. O. and SYKES M. K. (1967) pH and blood-gas analysis. *Anaesthesia* **22**, 575–597.

ASKROG V. (1966) Changes in (a-A)CO_2 difference and pulmonary artery pressure in anesthetized man. *J. Appl. Physiol.* 21, 1299–1305.

[illegible]DINGHAM I. MCA., PARR[illegible] (1972) Myo- cardial blood flo[illegible] shock [illegible]
LEDINGHAM I. MCA. [illegible] Con[illegible] on 'Shock'. Lo[illegible] [illegible]
[illegible]OLLISON P. L. [illegible] 5th ed. Oxford, Bla[illegible]
[illegible]IE L. H. (1965) Effect [illegible] on function a[illegible] metabolism of isol[illegible] Am. J. Phys[illegible] 209, 1075–1080.
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Notice

A one-day instructional course on bull[illegible] wounds and explosive blast injuries will take place on Wednesday 25 Ap[illegible] 1979 at The Royal Army Medical College, Millbank, London SW1.

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arter[illegible] output was [illegible] 95 per c[illegible] [illegible] that for sy[illegible] was $r = 0.54$ with [illegible] 0·24 and 0·75. The r[illegible] before reinfusion of [illegible] reinfusion to 0·89 ± [illegible] ($P < 0.03$).

Discussion

Six phases of haemodynamic and metabolic change were recognized during the reinfusion of shed blood and shortly thereafter. However, the existence of these phases must be accepted with the same provisos mentioned in the previous paper. Reinfusion of shed blood resulted in an immediate improvement in haemodynamic status, with restoration of tissue perfusion as evidenced by the elevation of oxygen consumption and carbon dioxide production. The latter can be attributed to the return of tissue metabolism toward normal, the metabolism of 'excess' lactate formed during anaerobic glycolysis, the mobilization of carbon dioxide from previously poorly perfused tissues and the interaction of infused acid citrate and circulating bicarbonate. These last two factors increase carbon dioxide production relative to oxygen consumption, and this explains the increase in respiratory quotient. The rise in $Pa\text{CO}_2$ secondary to the rise in carbon dioxide production would have been greater but for the reduction in physiological dead space, which improved the efficiency of carbon dioxide excretion.

Oxygen consumption ceased to increase after phase II, while haemodynamic improvement persisted up to and including phase IV. This suggests that tissue perfusion had become maximally effective long before haemodynamic improvement was complete and the return of all the shed blood. As opposed to the early restoration of tissue blood flow, arterial pH did not rise above the pre-infusion level until phase V.

The data in *Table III* indicate that with the reinfusion of shed blood there is an initial tendency for arterial pH to fall; this was principally the result of a rise in $Pa\text{CO}_2$, because there was only a minimal change in base excess. The finding that buffering capacity at this time was little changed may be explained by the counterbalancing of two tendencies; the tendency for buffering capacity to be reduced by anaerobic metabolites entering the general circulation, by infused acid citrate and by metabolism of citrate ions; and the reverse tendency attributable to the metabolism of 'excess' lactate and the neutralization of acid citrate. Because ventilation remained constant and the physiological dead space ratio was not increased, the rise in $Pa\text{CO}_2$ at this time was secondary to the previously described increase in carbon dioxide production. Thus, the initial downward trend of arterial pH is primarily the consequence of increased carbon dioxide production and not of reduced buffering capacity. Identical mechanisms operating in reverse were identified during initial bleeding in the previous study; arterial pH rose because carbon dioxide production was reduced, there being no increase in buffering capacity (Pardy and Dudley, 1979).

As further shed blood was returned, $Pa\text{CO}_2$ began to fall and buffering capacity increased, causing arterial pH to rise. The reduction in $Pa\text{CO}_2$ towards the pre-infusion level was not caused by a decrease in [illegible] production but by a fall in physi[illegible] [illegible] With regard to buffering capacit[illegible] [illegible] would have been operating as w[illegible] [illegible] except that the mobilization [illegible] would probably have be[illegible] [illegible] Therefore, the increase in buffer[illegible] capacity [illegible] principally the result [illegible] 'excess' [illegible] An outline of th[illegible] mechanisms is given [illegible]

The data in this study [illegible] the stateme[illegible] previously made about physiological dead sp[illegible] (Pardy and Dudley, 1979). Certain haemodynam[illegible] inferences of clinical relevance can also be made. Th[illegible] marked improvement in cardiovascular performanc[illegible] after the infusion of blood for only 4 min demonstrates that even a small degree of blood volum[illegible] restoration may be efficacious. The patient in haemo[illegible]rhagic shock should therefore be infused as soon a[illegible] possible with whatever suitable fluid is availabl[illegible] albeit the volume immediately to hand is sma[illegible] (Dudley et al., 1968).

A second point is that while the measurement of arterial pH may permit evaluation of the severity of haemorrhagic shock, the finding of a low pH does not necessarily mean that alkalis should be infused (Andersen et al., 1967). As seen in the current study, restoration of blood volume is associated with spontaneous return to normal of arterial pH, but this may occur quite a long time after haemodynamic recovery. It is to be noted that myocardial contractility in the intact animal (Downing et al., 1965) and in the isolated heart (Opie, 1965) is not impaired until pH falls below 7·1 and raising arterial pH from 7.00 to normal does not improve myocardial action in the acidotic dog (Ledingham et. al., 1972). Nevertheless, pH may fall sharply with initial volume replacement, and in our study arterial pH fell by 0·17 and 0·08 respectively in 2 animals. The likelihood of such a fall in pH is greater when blood volume replacement is rapid.

Therefore, should arterial pH be in the region of 7·1 before resuscitation, it is suggested that blood should not be infused unduly rapidly in the first instance, and that the concomitant administration of a small amount of sodium bicarbonate may be advantageous. If arterial pH is not below 7·2, however, the use of bicarbonate in the hypovolaemic subject without other causes for acidosis (such as dead or damaged tissue) should be restricted.

Finally, the measurement of pulmonary artery pressure would appear to be of greater value than that of systemic arterial pressure in the assessment of both active bleeding (Pardy and Dudley, 1977) and of the effectiveness of blood volume restoration.

Acknowledgement

This work was made possible by support from the Wellcome Trust.

References

ANDERSEN M. N., BORDER J. R. and MOURITZEN C. V. (1967) Acidosis, catecholamines and cardiovascular dynamics: when does acidosis require correction? *Ann. Surg.* **166**, 344–356.

DOWNING S. E., TALNER N. S. and GARDNER T. H. (1965) Cardiovascular responses to metabolic acidosis. *Am. J. Physiol.* **208**, 237–242.

DUDLEY H. A. F., KNIGHT R. J., MCNEUR J. C. and ROSENGARTEN D. S. (1968) Civilian battle casualties in South Vietnam. *Br. J Surg.* **55**, 332–340.

Table II. CHANGES DURING [illegible]

	(n = 9)					VI (n = 2)
Mean systemic arterial	12±[illegible]	[illegible]	[illegible]	[illegible]	[illegible]§	1±1
pressure (%)	50±[illegible]	[illegible]	[illegible]	[illegible]	[illegible]8†	89±0
Cardiac output (%)	8[illegible]	[illegible]	[illegible]	[illegible]	[illegible]16§	−13±8
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]±17†	75±24
Total peripheral	9	±4	[illegible]	[illegible]	7±25§	24±5
resistance (%)	[illegible]	±77	[illegible]	[illegible]	134±31§	127±42
Mean pulmonary artery	[illegible]	9±4*	[illegible]	5[illegible]	−2±17§	−27±18
pressure (%)	[illegible]	53±11*	62±11*	74±11*	101±12‡	93±17
Pulmonary vascular	−48±[illegible]2‡	−42±69§	−11±32§	−42±32*	−16±57§	−5±9
resistance (%)	337±183	283±145‡	247±100*	241±89*	207±70†	103±26
Oxygen consumption	11±7*	6±4*	−1±9§	1±7§	0±3	−6±3
(%)	86±12	97±10*	103±11*	102±12*	101±14†	93±8
Carbon dioxide production (%)	12±7*	5±4‡	5±5‡	3±8§	−5±15§	−8±14
	87±17	99±16*	105±17*	109±17*	108±19†	104±23
pH arterial blood	−0·02±0·03§	0·00±0·02	0·01±0·02§	0·03±0·01*	0·05±0·03†	0·04±0
	7·32±0·07	7·29±0·07§	7·29±0·08§	7·30±0·09§	7·32±0·11§	7·37±0·01
P_{CO_2} arterial blood	4±3*	1±2§	−1±2§	−1±2§	−3±6§	−5±0
(mmHg)	42±5	45±6*	46±8†	46±9§	44±11§	42±8
Base excess (mmol/l)	−0·3±1·6§	−0·3±1·3§	0·4±1·3§	1·3±0·6*	2·1±1·0†	0·6±0·4
	−4·8±3·3	−5·0±3·5§	−5·4±3·4§	−4·9±3·7§	−3·8±4·2§	−1·7±3·0
Total venous admixture	0±3	1±3§	2±2§	5±6*	−2±5§	−1±1
(%)	8±5	9±5§	10±6§	12±7§	17±7‡	7±5
Physiological dead space	−2±2§	−2±1*	−2±2§	−2±3§	1±7§	−3±6
ratio (%)	60±6	58±6§	57±7‡	55±6*	52±9†	57±1

All values are mean ±s.d. Percentage values (except for total venous admixture and physiological dead space ratio) are of the pre-bleed level.
The first figure is the change during the phase, the second figure is the value at the start of the phase.
* $P<0·01$; † $P<0·02$; ‡ $P<0·03$; § not significant.

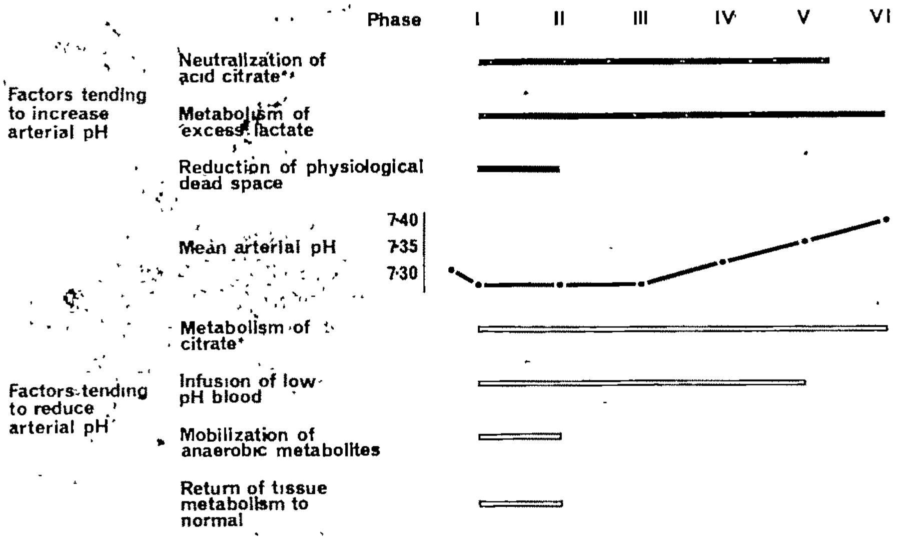

Fig. 1. Factors tending to influence blood pH in the hypovolaemic animal during resuscitation with blood anticoagulated with acid–citrate–dextrose. *Acid–citrate–dextrose contains sodium acid citrate (disodium hydrogen citrate) prepared by the interaction of nitric acid and sodium citrate (trisodium citrate). On infusion, sodium acid citrate is neutralized by sodium bicarbonate with the release of carbon dioxide and the remaining sodium citrate is metabolized by the liver.

Phase III

The haemodynamic improvement continued, but there was no further change in oxygen consumption.

Phase IV

Pulmonary artery pressure now rose sharply and base excess, arterial pH and total venous admixture increased.

Phases V and VI

The only prominent changes in these phases were the continued increases in base excess and arterial pH.

The correlations between pulmonary artery pressu[illegible] and cardiac output and between systemic arteri[illegible] pressure and cardiac output during the reinfusion of shed blood were determined; that for pulmonar[illegible]

Br. J. Surg. Vol. 66 (1979) 89–9

Sequential patter[illegible] metabolic changes in expe[illegible]volae[illegible]ck.
II. Responses to [illegible] shed [illegible]

B. J. PARDY AND H. A. F. DUDLEY*

SUMMARY

The haemodynamic and metabolic effects which follow the infusion of blood in experimental hypovolaemia have not been studied in detail. The 10 dogs that survived 90 min of hypovolaemia in a study of bleeding (Pardy and Dudley, 1979) were investigated during and shortly after the reinfusion of shed blood using the same techniques.

Data from 9 animals were suitable for analysis. As with bleeding, 6 sequential phases were identified; reinfusion of blood was completed in the fifth phase. Initial reinfusion was associated with a rapid improvement in haemodynamic and metabolic status, although mean arterial pH fell because carbon dioxide production increased. Maximum metabolically effective tissue perfusion was probably attained in phase II, but haemodynamic improvement continued until phase IV. Arterial pH did not rise above the pre-infusion value until phase V, and this rise was the result of a fall in $Pa\text{CO}_2$ *secondary to a reduction in physiological dead space and an increase in buffering capacity.*

Pulmonary artery pressure was superior to systemic artery pressure as a predictor of cardiac output during blood volume restoration. A number of conclusions pertaining to clinical practice are drawn.

WHILE the haemodynamic and metabolic changes during established hypovolaemic shock have been intensively studied and the findings widely reported, few data are available on the exact sequence of events during resuscitation from this state. We therefore continued the study described in our previous paper (Pardy and Dudley, 1979), and analysed in similar detail the changes during and shortly after the reinfusion of shed blood.

Materials and methods

The 10 greyhounds that survived the acute haemorrhage study were reinfused with shed blood previously collected in sterile, airless plastic bags containing acid–citrate–dextrose (NIH Solution A; Mollison, 1972). The warmed blood was returned as a drip infusion via a standard giving set into a peripheral vein at a rate of approximately 30 ml/min. No other fluid was infused.

Analyses of cardiorespiratory and metabolic function were performed as described in the previous study before and 4, 10, 20, 40 and 80 min after starting the reinfusion of shed blood. Values of statistical significance were determined using the Walsh non-parametric test for related samples (Siegel, 1956).

Results

All dogs survived the period of resuscitation from shock, but at the end of the experiment systemic arterial pressure was declining in 3 animals (results from these dogs acquired during the first 40 min only have been used). All results are reported as mean ± s.d. and percentage values for indices other than total venous admixture and physiological dead space ratio are of the pre-bleed value. The data from one animal were discarded because the pre-infusion systemic arterial pressure was 78 per cent whereas the mean systemic arterial pressure for the other 9 dogs was 50±9 per cent. Absolute values for the various indices before reinfusion of blood are given in *Table I*.

The duration of the reinfusion period was 53±17 min, and the resultant cardiorespiratory changes could be separated into six sequential phases. The factors determining placement of results in the various phases are shown in *Table II* and the cardiopulmonary and metabolic data are given in *Table III*.

Table I: ABSOLUTE VALUES BEFORE REINFUSION OF SHED BLOOD (mean±s.d.)

Mean systemic arterial pressure (mmHg)	82±11
Cardiac output (ml min^{-1} kg^{-1})	54±21
Total peripheral resistance index (dyn s kg cm^{-7})	1435±492
Mean pulmonary artery pressure (mmHg)	8±5
Pulmonary vascular resistance index (dyn s kg cm^{-7})	160±102
Oxygen consumption (ml kg^{-1} min^{-1})	6·6±1·6
Carbon dioxide production (ml kg^{-1} min^{-1})	5·4±1·7
pH arterial blood	7·32±0·07
$P\text{CO}_2$ arterial blood (mmHg)	42±4·6
Base excess (mmol/l)	−4·8±3·3
Total venous admixture (%)	8±5
Physiological dead space ratio (%)	60±6

Table II: FACTORS DETERMINING PLACEMENT OF DATA IN THE VARIOUS PHASES

	Relation to reinfusion of shed blood
Phase I	First 4 min
Phase II	4–10 min
Phase III	10–20 min
Phase IV	20–40 min, but not including dogs in which infusion was completed
Phase V	Dogs in which infusion was completed (40–80 min in 5 animals, 20–40 min in 1)
Phase VI	After infusion completed (40–80 min)

Phase I

During the first 4 min, cardiac output rose and pulmonary vascular resistance fell. There were consequent rises in systemic arterial pressure and mean pulmonary artery pressure, and $Pa\text{CO}_2$, oxygen consumption and carbon dioxide production increased.

Phase II

The haemodynamic and metabolic changes of phase I continued except that there were no further significant changes in pulmonary vascular resistance or $Pa\text{CO}_2$. The physiological dead space ratio fell. Analysis of the combined changes during phases I and II showed that there was a significant fall in total peripheral resistance by 32±35 per cent ($P<0·03$), and that the fall in arterial pH was not significant.

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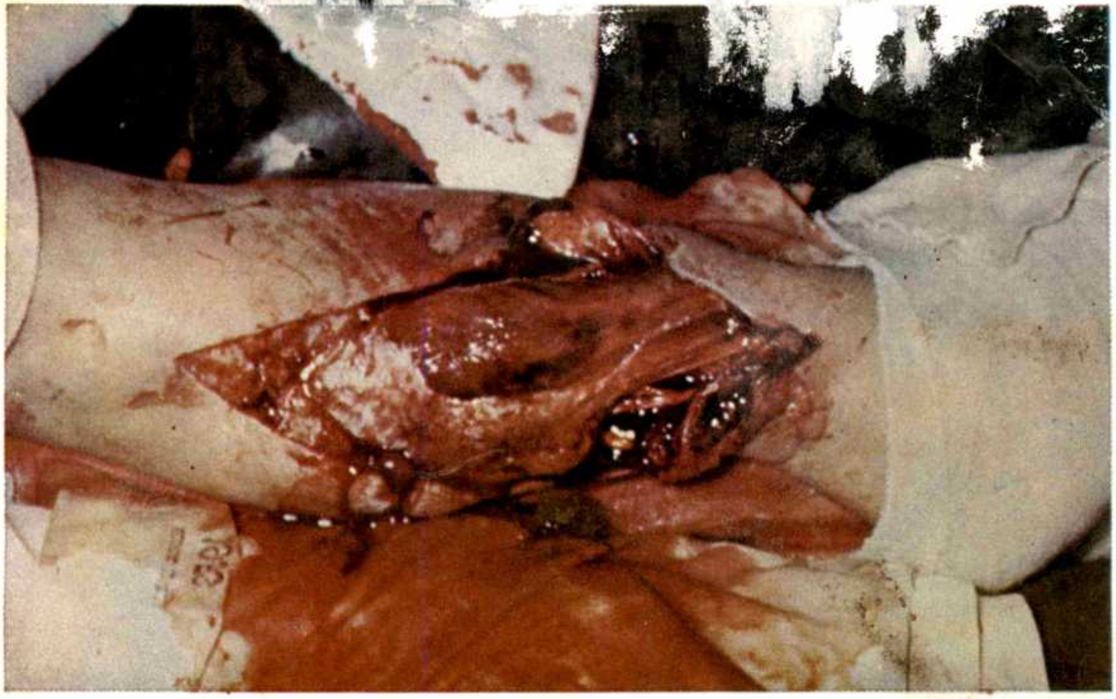

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through nique sphincte ure*

E†

sults a p hrough techn try. The first part of the work of the reproducibility of this technique using both an infused tube system and a system of subminiature, intraluminal strain gauge transducers. The second part of this report describes a study into the effect that the position of the recording hole on the probe may have in relation to the measured pressure for the lower oesophageal sphincter.

THERE is no doubt that there is a zone of increased pressure situated at the lower end of the oesophagus which acts as a barrier to the regurgitation of gastric contents into the oesophageal lumen. Unfortunately, the accuracy of measurement of this lower oesophageal sphincter pressure presents a significant problem (Pope, 1970; Perez-Avila and Irvin, 1975) and therefore its clinical use is precluded at present. There are two major sources of error, measurement artefact and measurement insensitivity (Dodds et al., 1976).

We have reassessed the reproducibility of lower oesophageal sphincter pressure as measured by the station pullthrough technique using an open-ended, water-infused manometry system and an oesophageal probe equipped with three subminiature, intraluminal strain gauge transducers—the Sensotec EMP3.

One suggested cause of recording infidelity is the actual position of the recording sites on the oesophageal probe (Kaye and Showalter, 1971). To study this we have looked closely at the effect that this has upon the recorded pressure for the lower oesophageal sphincter.

Materials and methods

Equipment

The first part of the study, on the reproducibility of the station pullthrough technique, was performed using two sets of equipment. In one series of studies a triple-lumen polyvinyl recording catheter of 4·5 mm diameter had side holes cut at 5, 10 and 15 cm from the tip (probe A, *Fig.* 1). It was connected to three Statham P23 pressure transducers and each lumen was infused at a constant rate of 27 ml/h by a Braun infusion pump (*Fig.* 2). The pressure variations were recorded on paper by a Grass Polygraph Model 7D eight-channel recorder, to which was also connected a temperature probe placed in the external nares. This effectively monitored the phases of respiration. The subject was asked to indicate when he swallowed by pushing a button.

In the other series of reproducibility tests a pressure probe equipped with three subminiature strain gauge transducers (Sensotec EMP3) was used (probe B, *Fig.* 1). Because this equipment had no infusion apparatus it could be plugged directly into the recording equipment.

In the study that investigated the effect of the position of the recording side hole upon the measured lower oesophageal sphincter pressure, two similar triple-lumen recording catheters were used (tubes 1 and 2 in *Fig.* 1). These were similar to the infusion probe that was used in the first study except that the three recording side holes all lay at the same level in each tube. In tube 1 they lay at 5 cm from the tip and in tube 2 they lay 15 cm from the tip.

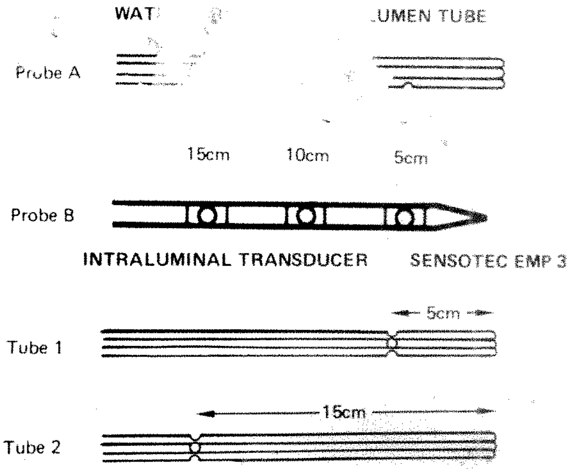

Fig. 1. Distal ends of probes. Probes A and B used in reproducibility study. Tubes 1 and 2 used in study on effect of location of recording side hole.

Table I: SUBJECTS STUDIED

	No.	Age (yr) Mean	Age (yr) Range
Reproducibility study			
Infusion probe	9 (7 M, 2 F)	23·1	21–35
Intraluminal transducer probe	8 (7 M, 1 F)	25·0	23–25
Side hole position study	11 (9 M, 2 F)	23·9	20–33

Subjects (*Table I*)

All subjects were volunteers whose mean age was 24 years (range 20–35 years). None had symptoms suggestive of oesophageal reflux or dyspepsia and informed consent was obtained in each case. The tests were performed after a 4-h fast during which time smoking was also forbidden. In the reproducibility study there were 17 subjects. Nine were tested with the open-tube system and 8 with the Sensotec equipment. Each subject was tested with the same equipment on three occasions. On the first day (day 1) two tests were performed, at 0830 h and again at 1630 h. A further test was performed a week later (day 7), again at 0830 h.

In the second part of the study there were 11 subjects, each of whom was tested on two occasions, once with each tube (1 and 2). These two tests were performed in random order on the same day.

Technique

In all tests the probe (infusion catheter or intraluminal transducer) was passed via the mouth until all three recording sites lay in the gastric lumen (*Fig.* 2). The subject then rested for 15 min. A standard station pullthrough was performed in each case as the patient lay on a couch. The probe was withdrawn 0·5 cm at a time through the lower oesophageal

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* Based upon communications read to the Surgical Research Society in July 1976 and to the British Society of Gastroenterology in September 1977.

† Department of Surgery, Hope Hospital (University of Manchester School of Medicine), Salford, Lancs.

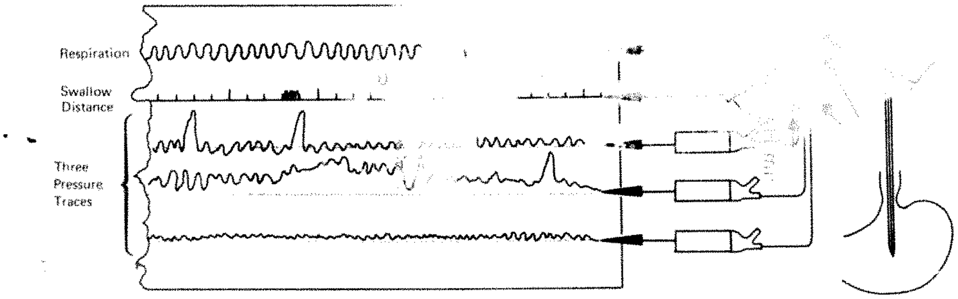

Fig. 2. The equipment.

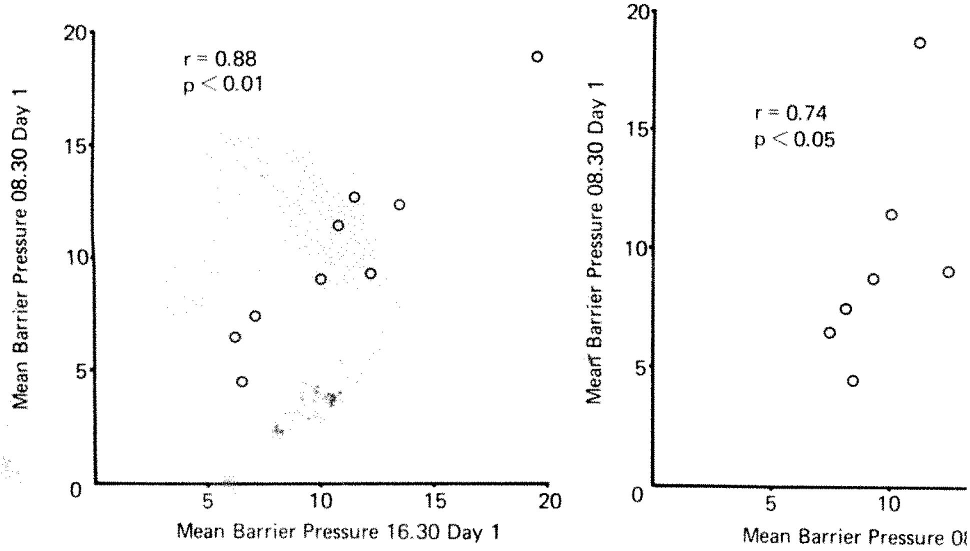

Fig. 3. Correlation of lower oesophageal sphincter pressure from occasion to occasion, using infusion syst

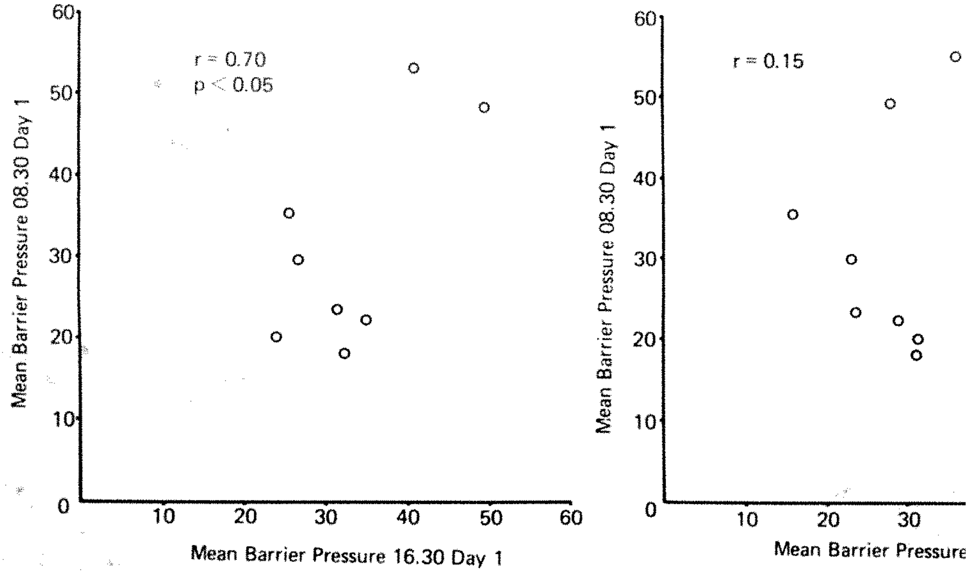

Fig. 4. Correlation of lower oesophageal sphincter pressure from occasion to occasion, using the intralumi system.

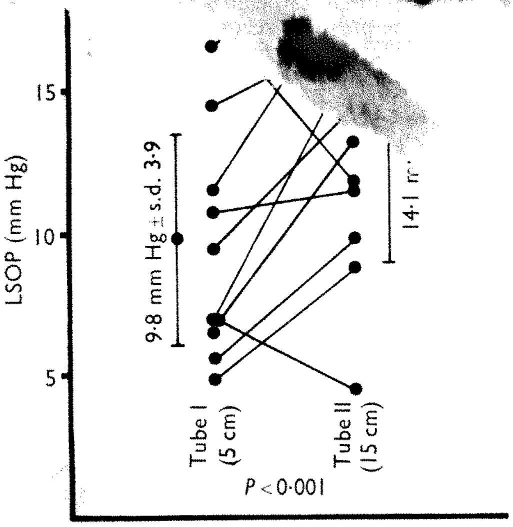

Fig. 5. Effect of side hole location on lower oesophageal sphincter pressure (LOSP).

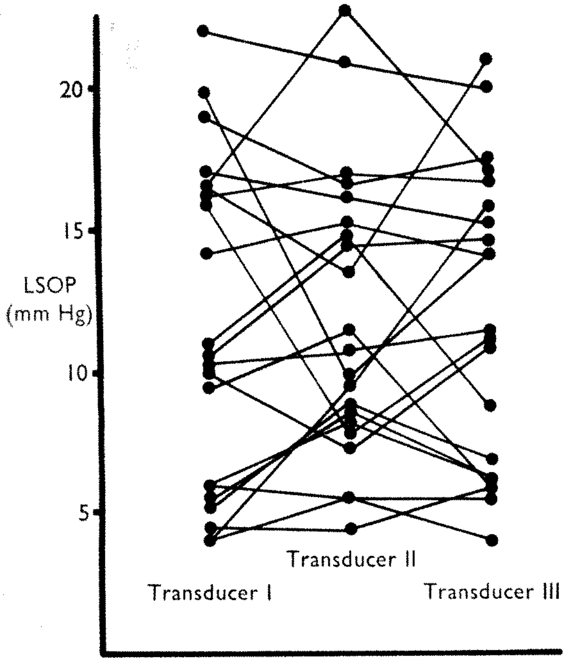

Fig. 6. Inter-transducer variation in lower oesophageal sphincter pressure (LOSP) around circumference of sphincter.

sphincter into the body of the oesophagus. A minimum of five respiratory cycles was allowed at each station.

Analysis of traces and statistical methods
The lower oesophageal sphincter pressure was taken as the difference between the mean end-expiratory value of the pressure in the sphincter and the mean end-expiratory value of the resting gastric pressure. It was expressed in millimetres of mercury.

Table [illegible]TS WITH INFUSED CATHETER

	Lower oesophageal sphincter pressure (mmHg)		
	Day 1 0830 h	Day 1 1630 h	Day 7 0830 h
[illegible]	7·4	7·15	8·15
[illegible]	[illegible]	10·1	12·4
3	[illegible]4	10·7	10·0
4	9·3	12·3	8·7
5	8·9	19·6	11·3
6	[illegible]·6	6·3	7·5
7	4·5	6·6	8·5
8	12·8	14·0	20·6
9	14·8	16·0	16·0
Mean ± s.d.	9·68 ± 3·43	11·34 ± 4·39	12·52 ± 5·07

Table III: RESULTS WITH INTRALUMINAL TRANSDUCER

	Lower oesophageal sphincter pressure (mmHg)		
Subject	Day 1 0830 h	Day 1 1630 h	Day 7 0830 h
10	35·2	25·6	16·2
11	20·1	23·8	31·6
12	22·5	34·4	28·9
13	53·1	40·6	36·4
14	48·4	49·0	28·0
15	23·2	31·0	24·2
16	18·1	31·8	31·2
17	29·9	26·5	23·2
Mean ± s.d.	31·4 ± 13·3	32·8 ± 8·3	27·5 ± 6·2

In the reproducibility study the results on different occasions were compared using correlation graphs. In the study on the effect of the side hole position, the results were compared using a paired Student's *t* test.

Results

Reproducibility of the station pullthrough technique
Using the infused manometry catheter there were no differences in the values obtained for the lower oesophageal sphincter pressure when a group of normal subjects was examined from occasion to occasion (*Table II*). A similar pattern emerged when the results obtained using the intraluminal transducer probe were examined, although the actual values were considerably higher (*Table III*). Using either system, however, the values obtained from occasion to occasion in any individual subject often varied considerably. The effect of this variation upon the reproducibility of the lower oesophageal sphincter pressure was assessed by correlating the values obtained from occasion to occasion in each individual. With the infusion system (*Fig.* 3) the reproducibility obtained from occasion to occasion on the same day was very satisfactory ($r = 0·88$), this being significant ($P < 0·01$). However, the correlation between the lower oesophageal sphincter pressure results measured on different days was not as good ($r = 0·74$), although this was still significant ($P < 0·05$). When the results from the intraluminal transducer system were evaluated (*Fig.* 4), although the reproducibility obtained from the two tests performed on the same day was significant ($P < 0·05$), the actual correlation ($r = 0·70$) was not as good as that obtained either from hour to hour or from day to day with the infusion

catheter system. Furthermore, there was no correlation at all between the lower oesophageal sphincter pressure measured from day to day with the intraluminal transducer system ($r = 0{\cdot}15$).

Recording side hole position
With tube 1, the mean l[illegible] sphincter pressure was 9·8 mm [illegible] With tube 2, the pressure w[illegible] s.d. 5·0, the difference between [illegible] of results being significant ($P<0{\cdot}001$). T[illegible] and 2 also enabled us to study the pressures in three different arcs of the circumference of the lower oesophageal sphincter (*Fig.* 6). It can be seen that in any one station pullthrough there was considerable variation between the results for the three pressure channel recordings in that test, and that this variation followed no particular pattern.

Discussion
The results of this study indicate that despite the advent of sophisticated electronic miniaturized pressure monitoring equipment such as intraluminal strain gauge transducers, the measurement of lower oesophageal sphincter pressure as recorded by the station pullthrough technique is more reproducible using a water-infused catheter system. In fact, the results we obtained with this latter, essentially simple, equipment were more reproducible from day to day than those obtained from hour to hour on the same day with the subminiature strain gauge transducers. This is very disappointing because the water-infused catheter system can be affected by a number of factors that influence recording fidelity (Dodds et al., 1976). One point worthy of emphasis is that our infusion catheter technique differed from the generally accepted standard technique as described by Stef et al. (1974) only in that we deliberately used a very low infusion rate of 27 ml/h for each pressure channel. Pope (1970) has confirmed that a slow infusion rate is satisfactory for examining the lower oesophageal sphincter.

Theoretically the intraluminal transducer probe (Sensotec EMP3) offers several advantages over the infusion catheter system. All the cumbersome plumbing is eliminated and since hydrostatic pressure effects no longer apply, the subjects can be tested in any convenient position (Dodds et al., 1976). However, the equipment required a long warm-up period, and as it was very temperature-sensitive, it had to be standardized at body temperature and not room temperature before use. It was very liable to baseline drift during the course of a recording session. Furthermore, the resultant traces showed a lot of superimposed high-frequency wave forms which made them much more difficult to interpret than those obtained from the infusion catheter system. This particular problem is one reason why the reproducibility of the station pullthrough with the intraluminal transducer probe was so poor. It may be that electronic filtering of this background noise would improve the quality of the recordings in the same way as the inherent damping of the infusion system probably does.

The fact that the intraluminal transducer probe recorded consistently higher pressures in the lower oesophageal sphincter than did the infusion system is not of any great importance. It is well recognized that dif[illegible]d differing pressures f[illegible]cter pressure (Earlam, [illegible] catheter system, we noted a differ[illegible] recorded both on the same d[illegible] in the individual subjects. [illegible]ngs of Perez-Avila and Irvin [illegible]y that there is a considerable [illegible]riation in the lower oesophageal sphincte[illegible]nal subjects. This is a finding which Pope (197[illegible]) has noted on many occasions. Despite this variation in sphincter pressure, however, we have demonstrated adequate reproducibility using an infused catheter system for measuring lower oesophageal sphincter pressure by the station pullthrough technique.

The second part of our study shows that the actual siting of the recording orifice in an infusion catheter system is important. The pressure is significantly higher when the side hole is situated more proximally than when it is located near the tip of the assembly. The reason for this difference is not clear. Suggestions that it is an artefact consequent upon angling of the tube against the lesser curvature of the stomach and thus the right side of the oesophageal sphincter cannot be correct. First, the catheter lumen distal to each of the recording side holes was occluded and therefore had no effect upon the pressures recorded. Secondly, the higher pressures were recorded by all three recording channels in tube 2 and thus were recorded from the circumference of the sphincter. We believe that the presence of a longer tail of infusion catheter lying in the gastric lumen below the recording holes may act as a stimulus to increase sphincter tone.

In the second part of the study we also noticed a considerable inter-transducer variation in the pressure recorded in any one test, in spite of the fact that all the recording orifices were arranged at the same level circumferentially, either at 5 or 15 cm from the tip. This variation confirms the presence of asymmetry of tone around the circumference of the sphincter, as previously noted by Kaye and Showalter (1971). In our study we have shown that the variation may be random. At first sight this may seem odd, but since our tube is quite soft and pliable (unlike that used by Kaye and Showalter), we have no reason to expect that it will have any constant radial orientation in respect to the sphincter.

We have thus demonstrated that there are two sources of inter-transducer variation in the station pullthrough technique—side hole position and radial asymmetry. An interplay of these two sources of variation may have had an effect on the results of our reproducibility study. The open-tube system, using as it did three radially orientated side holes, recorded three values from the circumference of the sphincter, which were averaged out and so the effects of radial asymmetry were negated. With the subminiature electronic probe, however, where the transducers all lay down the same side, the results would depend on the radial orientation of the probe.

Finally, as a sphincter is sensitive to distension, then the mere presence of a probe of any sort in its lumen must cause some stimulation. Therefore, any recorded pressures are not true resting pressures. The work of Kaye and Showalter (1974) and Lydon et al. (1975) on the effect of the catheter diameter on recorded pressures would support this argument.

[illegible] on [illegible] technique when [illegible] r [illegible] is used to measure lower [illegible] pressure. In normal subje[illegible] minor variation of sphincter ton[illegible] and from day to day. Differe[illegible] grossly differing results, and [illegible] attempted then the same syste[illegible] each case. The length of the cathe[illegible]ably projecting into the stomach below the re[illegible]ng orifices affects the recorded value for the lower oesophageal sphincter pressure. We would recommend that in oesophageal manometry the recording side holes should be situated as close to the tip of the catheter as possible. Radial asymmetry is a further cause of recorded pressure variation, but its effects are largely negated by using a multi-lumen catheter system which thus records around the circumference of the sphincter.

Finally, we feel that work should be directed towards finding a method whereby the function of the lower oesophageal sphincter, and any other sphincter, can be assessed without attempting to force a foreign body through its lumen.

References

DODDS W. J., STEF J. J. and HOGAN W. J. (1976) Factors determining pressure measurement accuracy by intraluminal oesophageal manometry. *Gastroenterology* **70**, 117–123.

[illegible]RLAM [illegible] Gastro-oesophageal junction. In: *Clinical Tests* [illegible] *Oesophageal Function.* London, Crosley [illegible]s, pp. 1–21.

KAYE [illegible] J. P. (1971) Manometric configuration [illegible] sphincter in normal human subjects. [illegible] 223.

KAYE M. D. and [illegible] 1974 Measurement of pressure in th[illegible] sph[illegible]. The influence of catheter diameter. [illegible] **19**, [illegible]0–863.

LYDON S. B., DODDS W. J., HOGAN W. J. et al (1975) The effect of manometric assembly diameter on intraluminal oesophageal recording. *Dig. Dis.* **20**, 968–970.

PEREZ-AVILA C. and IRVIN T. T. (1975) Interpretation of lowe oesophageal pressure measurements. *Br. J. Surg.* **62**, 663.

POPE C. E. (1970) Effect of infusion on force of closure measurements in the human oesophagus. *Gastroenterology* **58**, 616–624.

POPE C. E. (1978) Personal communication.

STEF J. J., DODDS W. J., HOGAN W. J. et al. (1974) Intraluminal oesophageal manometry: an analysis of variables affecting recording fidelity of peristaltic pressures. *Gastroenterology* **67**, 221–230.

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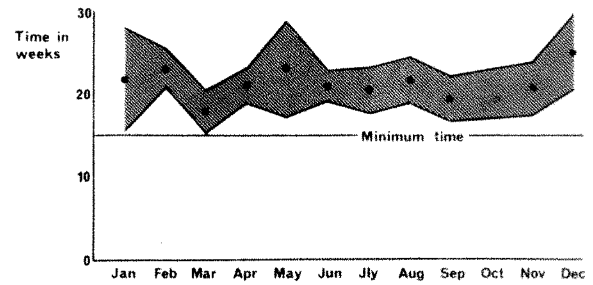

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The surgical management of [illegible] oesophagus and cardia: a revi[illegible] 292 patients treated over a 15-ye[illegible] -75)

J. W. JACKSON, D. K. C. COOPER, L. GUVEND[illegible] AND H. REECE-SMITH*

SUMMARY

Of 292 patients, excision of the tumour with replacement by stomach or jejunum was carried out in 216 in whom the lesion was considered operable on both technical and general grounds, intubation was performed in 45 and the remaining 31 were managed without operation.

Of the 216 in whom resection was performed, only 20 per cent were free from local spread, lymph node involvement or secondary deposits at the time of operation. Hospital mortality was 18 per cent and did not significantly differ between one 5-year period and another. Survival at 1 year was 54 per cent, at 2 years 25 per cent and at 5 years 14 per cent. The average length of survival following intubation was 2·6 months and following non-operative management 2·8 months. The poor average survival of between 3·5 and 5 months obtained in those patients with secondary deposits at the time of resection suggests that resection is of questionable value in this group.

There was a marked difference in survival following Roux loop procedures compared with upper partial gastrectomy for tumours of the lower third and cardia in patients without lymph node involvement or secondary deposits, strongly suggesting that upper partial gastrectomy, although a rather simpler and quicker operation, is not the operation of choice in these patients.

On 31 December 1976, after a minimum follow-up of 1 year, there were only 22 patients still alive of the original 292 (7·5 per cent).

DURING the 15-year period from 1 January 1961 to 30 December 1975, 292 patients with carcinoma of the oesophagus were admitted to Harefield Hospital under the care of one surgeon (J. W. J.). In many of these cases the tumour actually arose in the cardia of the stomach, but, as the presenting symptom (dysphagia) is frequently identical and as the surgical management is very similar, we have treated these two lesions as a single entity; indeed, in many cases it would be difficult, except possibly by histology, to localize the exact origin of the tumour. Throughout this period there was a consistent approach in the management of such patients. Operation involving excision of the tumour with replacement by stomach or jejunum was carried out whenever the lesion was considered operable on both technical and general grounds; 216 patients were thus treated. Of the remaining 76, 45 underwent some form of intubation procedure and 31 were managed without operation. Follow-up (to 31 December 1976) has been from 1 to 16 years.

Patients and methods

Patients

Sex incidence: Of the 292 patients seen, 169 were male (58 per cent) and 123 female (42 per cent), giving a male to female ratio of 1·4 : 1·0.

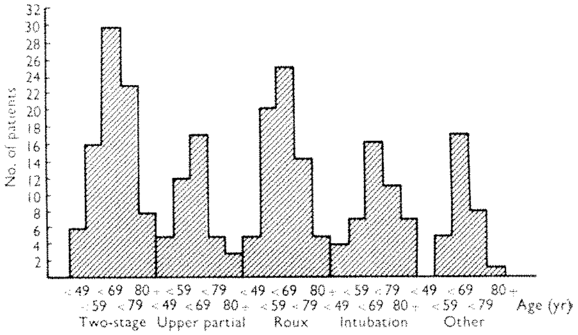

Fig. 1. Age of patient related to management.

Age incidence: The youngest patient seen was aged 27 years and the oldest 91 years with an average of 65 years. The greatest incidence was in the seventh decade of life (*Fig.* 1). The average age of the female patients (75 years) was considerably older than that of the male patients (58 years).

Presenting symptoms: In all but 30 patients (that is, in almost 90 per cent) the presenting symptom was dysphagia. Indigestion and loss of weight were other symptoms of importance. The duration of symptoms at the time when the patient was first seen at the hospital was from as short a period as 2 weeks to as long as 3 years (mean 22 weeks). There appeared to be no relation between the duration of symptoms and the operability of the lesion.

Site of tumour: No tumours of the cervical oesophagus were seen. It is customary to divide the thoracic oesophagus into three parts—upper (supra-aortic), middle (arch of aorta to inferior pulmonary vein) and lower (including the cardia of the stomach). Tumours of the lower third and cardia predominated (197 cases), though tumours of the middle third were also common (107 cases). Only 6 patients with a tumour confined to the upper third of the thoracic oesophagus were seen.

Tumours of the lower third and cardia were more common in men (125) than women (54) (male to female ratio of 2·5 : 1·0), whereas with tumours of the middle third the sex relationship was altered (men 41, women 66) (male to female ratio of 1·0 : 1·5). The relationship of the site and histology of the tumour to the sex of the patient can be seen in *Table I*.

Histology: The histology of the tumour was closely related to the site of origin (*Table I*). Squamous cell carcinoma predominated in the middle third of the oesophagus (87 of 107, 81 per cent), whereas adenocarcinoma was commonest in the lower third and cardia (116 of 179, 65 per cent). Twenty-four undifferentiated tumours were seen, fairly evenly distributed throughout the middle and lower oesophagus. One leiomyosarcoma occurred in the lower third and cardia, and in 3 cases the exact histological nature of the malignancy was not stated by the pathologist.

The number of patients seen during each of the three 5-year periods covered by the study (1961–5, 1966–70 and 1971–5) steadily increased from 68 during the first period, 102 during the second, to 122 during the third. Analysis of these patients reveals, however, that there was no statistical difference in the

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* Harefield Hospital, Middlesex.

Conclusions
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[illegible] AND [illegible] OGY OF TUMOUR TO [illegible] EX OF PATIENT

		[illegible]			Female			Total	
		[illegible]	[illegible]	[illegible] tumours	No. patients	% all tumours in women	% all tumours	No. patients	% all tumours
Upper third	Squam[illegible]	[illegible]	[illegible]	0·35	2	1·6	0·7	3	1·05
	Anaplast[illegible]	2	[illegible]	0·7	1	0·8	0·35	3	1·05
Middle third	Squamous	30	17[illegible]	10·3	57	46·3	19·5	87	29·8
	Adeno.	5	2·9	1·7	5	4·0	1·7	10	3·4
	Anaplastic	6	3·5	2·0	4	3·2	1·4	10	3·4
Lower third	Squamous	24	14·2	8·2	21	17·1	7·2	45	15·4
	Adeno.	89	52·6	30·5	27	22·0	9·2	116	39·7
	Anaplastic	9	5·3	3·0	5	4·0	1·7	14	4·7
	Other	3	1·8	1·0	1	0·8	0·35	4	1·35

sex ratio, duration or nature of symptoms, age distribution, site or histological incidence between one 5-year period and another.

Management
As dysphagia is such a distressing symptom, a fairly aggressive policy towards operative resection was followed. All patients were assessed initially with a barium swallow, oesophagoscopy and bronchoscopy. Only patients with a very advanced state of the disease where multiple secondaries were present or with extremely severe concomitant disease were excluded from operation on general grounds. Others were excluded on the grounds of technical inoperability where there was bronchial or tracheal involvement or evidence of direct local spread to other major organs such as the liver or lungs. In several cases the assessment of operability was finally made at laparotomy.

Intubation with a Celestin or Mousseau Barbin tube was performed in 45 patients with advanced disease. Four of these patients had been explored with a view to resection, which did not prove possible; in the remaining 41 patients intubation was a primary procedure. In 31 patients dilatation alone (8 cases), and/or radiotherapy (12 cases), together with palliative medical care, were the only measures considered applicable. In 10 of these patients exploratory surgery had been carried out initially and in 1 a temporary feeding gastrostomy was fashioned.

Of those patients in whom the tumour was considered resectable on both technical and general grounds, 1 patient with a tumour of the upper third of the oesophagus underwent a three-stage oesophagectomy with replacement by stomach, the oesophagogastric anastomosis being performed in the neck.

Eighty-three patients with a middle third tumour underwent a two-stage oesophagectomy with replacement by stomach, the anastomosis being performed through a right thoracotomy.

Patients with tumours of the lower third and cardia underwent a one-stage oesophagectomy through a left thoraco-abdominal incision when either a partial oesophagectomy and upper partial gastrectomy with oesophagogastric anastomosis was performed (63 patients) or a partial oesophagectomy and total gastrectomy with replacement with Roux-en-Y loop of jejunum was carried out (69 patients). The decision to perform an upper partial gastrectomy rather than a total gastrectomy was based on a number of factors, the most important of which was the presence or absence of tumour in the abdominal oesophagus or cardia. In cases where the tumour did not involve these regions an upper partial gastrectomy was performed. If the oesophagogastric junction or cardia was involved, a total gastrectomy was considered essential.

All anastomoses were performed using two layers of interrupted linen thread sutures.

The percentage of patients in whom resection procedures were performed varied little from one 5-year period to another, being 78 per cent (53 of 68) during 1961–5, 70 per cent (72 of 102) during 1966–70, and 75 per cent (91 of 122) during 1971–5. The resectability rate was identical in men and women (74 per cent).

Table II: EXTENT OF SPREAD AT TIME OF OPERATION

Op.	No local spread	Local spread only	Lymph node involvement	Secondary deposits	Total
T.-s. O.	19 (22%)	8 (10%)	51 (61%)	5 (6%)	83
U.P.G.	18 (28%)	3 (5%)	38 (60%)	4 (6%)	63
R.L.*	6 (9%)	2 (3%)	55 (79%)	4 (6%)	67*
Total	43 (20%)	13 (6%)	144 (67%)	13 (6%)	213*† (99%)

Op., operation; T.-s. O., two-stage oesophagectomy; U.P.G., upper partial gastrectomy; R.L. Roux loop; Int., intubation.
* In 2 further cases the extent of spread was not stated.
† One further patient underwent a three-stage oesophagectomy (no local spread).

Extent of disease at time of operation
Whether resection of the tumour was considered to be curative or palliative was of little importance, for whenever dysphagia was present, resection, where possible, was considered the treatment of choice; in any case, evidence as to whether the operation was likely to be curative or not was frequently not available until the procedure was well advanced or even until resected tumour specimen had been studied under the microscope.

The extent of the disease at the time of resection is shown in *Table II*. Only 20 per cent of the total of 216 were free from local spread, lymph node involvement or secondary deposits at the time of operation. In 6 per cent local spread had occurred through the full thickness of the oesophagus, 67 per cent had lymph node involvement, and in a further 6 per cent macroscopic secondary deposits in such organs as the liver were already present.

Results

Hospital mortality
The operative mortality in these elderly patients, who were often grossly wasted as a result of their inability to take in adequate nourishment over a period of weeks or months, was high. Of those undergoing a two-stage oesophagectomy, the hospital mortality—those patients dying within 30 days of operation—was 20 per cent (17 of 83). After upper partial gastrectomy it was 19 per cent (12 of 63), and after a Roux-en-Y jejunal loop procedure, 14 per cent (10 of 69). The 1 patient undergoing a three-stage oesophagectomy recovered well and left hospital after 22 days. This gives an overall hospital mortality of 18 per cent (39 of 216).

Table III: CAUSES OF EARLY POS[illegible] DEATHS

Op.	Respiratory	Cardiovascular	Surg	[illegible]	[illegible]
T.-s. O. (83)	8	6			
U.P.G. (63)	4	2			2†
R.L. (69)	4				10‡
Int. (45)	8				14§
Total (260)	25	10		11	53‖

For abbreviations see *Table II*.
Figures in parentheses in the first column are no. of patients.
Number with serious concurrent disease: * 8; † 2; ‡ 4; § 8; ‖ 26.

Table IV: RELATIONSHIP OF POSTOPERATIVE MORTALITY TO CONCURRENT DISEASE

Op.	Total patients	Patients with concurrent disease	Early deaths	Patients with concurrent disease dying
T.-s. O.	83	24 (29%)	17	8 (47%)
U.P.G.	63	12 (19%)	12	2 (17%)
R.L.	69	10 (14%)	10	4 (40%)
Total	215	46 (21%)	39	14 (36%)

For abbreviations see *Table II*.

Table V: HOSPITAL MORTALITY RELATED TO AGE

Age (yr)	Total patients	Patients dying within 30 d of op.	Hospital mortality (%)
<49	21	2	10
50–59	60	8	13
60–69	105	16	15
70–79	78	17	22
80<	28	10	36
Total	292	53	18

Table VI: MAJOR NON-FATAL POSTOPERATIVE COMPLICATIONS

Op.	Respiratory	Surg.	Wound infection	DVT/ PE*	Other	Total
T.-s. O. (83)	11	5	5	1/1	4	27† (28%)
U.P.G. (63)	6	1	4	4/2	4	21‡ (30%)
R.L. (69)	3	3	6	3/1	2	18§ (23%)
Total (215)	20	9	15	8/4	10	66‖ (27%)

* If the pulmonary embolus was secondary to the deep vein thrombosis (DVT) it was recorded as a pulmonary embolus (PE) only.
† In 23 patients. ‡ In 19 patients. § In 17 patients. ‖ In 59 patients.
For abbreviations see *Table II*.

Table VII: AVERAGE LENGTH OF POSTOPERATIVE STAY IN HOSPITAL IN DAYS

Operation	1961–5	1966–70	1971–5
Two-stage oesophagectomy	30	26	16
Upper partial gastrectomy	27	26	19
Roux loop	30	24	19
Intubation	29	22	17
Average for all patients	30	25	18

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41 not explored in whom intubation w
procedure, 13 died (32 per cent mortalit
of early postoperative death are listed in
Amongst the patients undergoing re
monia (16 cases) was the most co
complication that led to death, in 5 case
known chronic bronchitics. Respir
rather than pneumonia, accounted for
whom had angina or features of hea
operatively.
Anastomotic leaks were factors in
only 5 patients, in 2 cases associated w
abscesses; as a fatal complication, lea
twice following Roux loop procedur
partial gastrectomy and once after a t
phagectomy. Other causes of death i
failure (3) and pulmonary emboli (1),
possible that emboli were also respon
of the cases of cardiac arrest or resp
mentioned above.
Of the patients undergoing intubati
(8 cases) and hepatic failure associated
deposits (3 cases) accounted for the ma
of hospital deaths.
The relationship between the incide
rent disease in each group, compared wi
in those who died, can be seen in *Table*
patients undergoing resection, 46 (21
significant concurrent disease, suc
bronchitis, heart disease, previous c
accidents or diabetes, at the time of op
teen of the 39 patients who died wit
operation had concurrent disease (35
patient undergoing a three-stage oesop
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There was an increased mortality w
age (*Table V*, *Fig*. 2). The slightly incr
for a two-stage oesophagectomy (20 p
one-stage procedure (17 per cent) ha
mentioned.

Major postoperative complications

Of those surviving resection, 59 patien
had between them a total of 66 majo
complications, fairly equally spread
three types of surgical procedure (*Tabl*
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following two-stage oesophagectomy
other two procedures. Postoperative ha
anastomotic leaks (3) and injuries t
laryngeal nerve (2, both associated
oesophagectomy) made up the 9 sur
tions. Prolonged paralytic ileus and
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Although the hospital [illegible] signific[illegible] improvement [illegible] stud[illegible] the length [illegible]s who survived t[illegible] period was reduce[illegible] [illegible]red with the earl[illegible]

Intubation [illegible] hospitalization as the more [illegible] resection.

Further procedures after resection

A proportion (30 per cent) of patients in all three operative groups required subsequent oesophagoscopy and dilatation. Thirty-three per cent of patients undergoing partial gastrectomy required oesophagoscopy and dilatation at some stage in their postoperative life, and the incidence following Roux loop procedures and two-stage oesophagectomy was 26 and 30 per cent respectively. In approximately two-thirds of these cases, dilatation was required to correct benign stricture formation at the site of anastomosis presenting as dysphagia and occurring early in the postoperative course (within a few weeks); this was generally easily managed by dilatation on one or two occasions. The other main indication for oesophagoscopy and dilatation was dysphagia resulting from local recurrence of tumour or from compression of the alimentary tract by enlarged infiltrated lymph nodes; dysphagia from these causes generally occurred later in the postoperative course and was frequently impossible to relieve, though dilatation, intubation and radiotherapy were each helpful on occasions.

Long term follow-up and survival

Of the original 292, 5 patients have been lost to follow-up. Four of these were patients in whom intubation had been performed and are therefore presumed to have died within a few weeks or months of the procedure. The fifth patient underwent a two-stage oesophagectomy. Follow-up (to 31 December 1976) has been from a minimum of 1 year to a maximum of 16 years.

Details of the percentage of patients still alive after each of the three types of procedure at 1, 2 and 5 years, excluding those dying in hospital postoperatively, are shown in *Table VIII*. The one patient subjected to a three-stage oesophagectomy survived for only 10 months. No patient in whom intubation was performed or who was managed by dilatation, radiotherapy, or other means survived for 1 year, the average length of survival for intubation being 2·6 months and for other forms of management 2·8 months.

If the numbers of patients surviving at 1, 2 and 5 years are considered as percentages of the overall number who *could* have survived as long, including those in whom resection was not performed, the survival curve, of course, drops even more sharply (*Fig*. 3). Survival at 1 year was only 32 per cent, at 2 years 15 per cent and at 5 years 5 per cent. Only 1 patient has to date survived for more than 10 years, a woman who is still alive and well almost 11 years after a two-stage oesophagectomy.

The percentage survival after resection and overall percentage survival are shown as actuarial curves in *Fig*. 3. There was no significant statistical difference between the 1-, 2- or 5-year survival for each of the

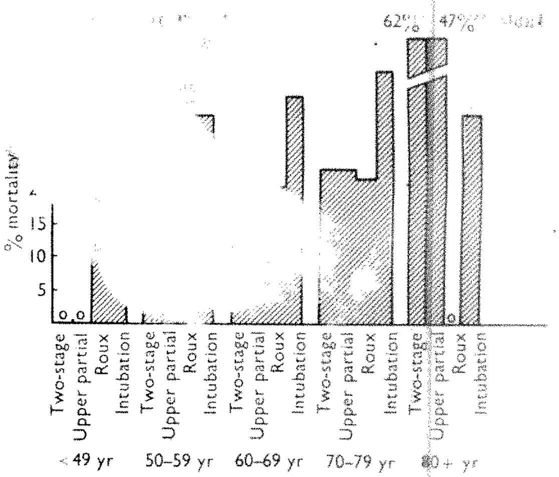

Fig. 2. Hospital mortality related to age at time of operation.

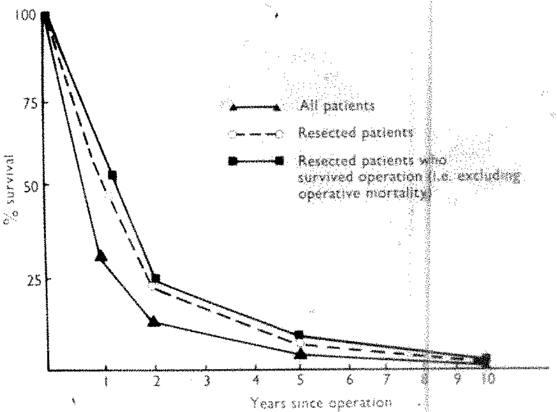

Fig. 3. Long term survival.

Table VIII: LONG TERM SURVIVAL FOLLOWING SUCCESSFUL RESECTION (i.e. EXCLUDING OPERATIVE MORTALITY)

	% patients			
Op.	1 yr	2 yr	5 yr	10 yr
T.-s. O.	58	27	17	3
U.P.G.	60	35	20	0
R.L.	49	22	11	0
Total	54	25	14	2

For abbreviations see *Table II*.

Table IX: AVERAGE SURVIVAL (mth) RELATED TO EXTENT OF DISEASE AT OPERATION

	Extent of spread at time of op.				
Op.	No local spread	Local spread only	Lymph node involvement	Secondary deposits	Total
T.-s. O.	49·6	30·9	17·5	5·0	26·5
U.P.G.	30·0	14·5	14·4	4·6	19·4
R.L.	42·2	34·5	15·9	3·5	18·9
Total	40·5	27·7	16·4	4·4	

For abbreviations see *Table II*.

three resection procedures. The average survival in months after each of the resection procedures in relation to the extent of the disease at the time of operation is shown in *Table IX*. As would be expected the length of survival is directly related to the ex[illegible] of the malignant process at operation. There [illegible] statistically significant difference b[illegible] length of survival between or[illegible]ure and another. Average overa[illegible]wing resection in women was 16·6 [illegible] and in men 18·3 months.

There was no significant difference in the length of survival of patients who presented with symptoms that had been present for longer than 12 weeks (14 months) when compared with those whose symptoms had been present for 12 weeks or less (13 months).

There was a marked difference in the average length of survival in patients with no local spread or local spread but no lymph node involvement between either two-stage oesophagectomy or Roux-en-Y loop procedures, on the one hand, and upper partial gastrectomy on the other. This is particularly important in regard to comparison of survival between those patients undergoing Roux loop procedures and those undergoing upper partial gastrectomy, as both operations were performed for tumours of the lower third and cardia.

On 31 December 1976, at which date there was a minimum follow-up of 1 year, there were only 22 patients still alive out of the original 292 (7·5 per cent).

Discussion

The overall predominance of males to females in the ratio of 1·4 : 1·0 correlates fairly well with the figures of the Registrar-General for 1968 (male to female, 1·5 : 1·0) and of McKeown (1972) (male to female, 1·7 : 1·0). From our own centre, Mullard (1960) reported his experience of 140 patients with oesophageal and cardiac tumours seen in the period 1948 to 1958; only 40 were women giving a male to female sex ratio of 2·5 : 1·0, suggesting that in recent years there has been a change in the sex ratio in this disease in the region served by Harefield Hospital.

The preponderance of women to men in carcinoma of the middle third of the oesophagus is unusual; men predominate in most other published series (Miller, 1961).

The age incidence of the patients in the present series correlates well with other published series (Miller, 1961; McKeown, 1972); the maximum incidence was in the seventh decade of life. The women were, however, on average 16·5 years older than the men at the time of diagnosis and treatment. The resectability rate, however, was identical in both sexes, and the average length of survival following resection showed no significant difference between men and women. Although the disease affects women at a later age than men, it appears that the behaviour of the tumour is not significantly different.

The presenting symptom was dysphagia in almost 90 per cent of patients; investigation by barium swallow and oesophagoscopy should be carried out whenever a patient presents with this symptom. Our observation that the length of history does not appear to affect the length of survival of the patient agrees with that of Leverment and Milne (1974); it can only be assumed that most patients do not attend their doctor until such time as the dysphagia is critical. Al[illegible]viously t[illegible] longer in slow-[illegible] is likely t[illegible]hese tumours have [illegible]ar stage as the faster growing tumours in patients who present earlier.

The close correlation of squamous cell carcinoma with the middle third of the oesophagus and of adenocarcinoma with the lower third and cardia is illustrated in the pr[illegible]ies, though not so clearly as in that reported [illegible]er (1961).

The fact that at the time of resection, and after exclusion of several patients on the grounds of either technical or general inoperability, 80 per cent of the patients showed evidence of local spread of the tumour, lymph node involvement or even distant metastases illustrates the difficulty in obtaining good long term results in this disease. In the majority of patients the tumour is already very advanced at the time of presentation.

The overall hospital mortality rate following resection of 18 per cent falls in the middle of the range of mortality rates in reported series from various surgical centres in the world (McKeown, 1973); mortality rates of 4·9 per cent to 35·7 per cent have been reported following oesophageal resection. Obviously the mortality rate is related to the selection of patients for operation. In the present series, where a fairly aggressive policy was followed in an effort to alleviate the very distressing symptom of total dysphagia in many patients, a moderately high mortality rate must be anticipated in elderly patients with advanced disease.

It was Collis's impression (1971) that hospital mortality declines as the experience of the surgeon and his team increases, although his own results supporting this view are not statistically significant except with regard to improvement following his first 50 operations performed in the early 1950s when the mortality was 52 per cent. In the present series there was no significant difference in hospital mortality between one 5-year period and another.

The high mortality associated with intubation (31 per cent) is surprising as this procedure is regarded as a simple surgical operation, and the deaths mainly reflect the extremely debilitated state of the patients; intubation was only performed in those patients deemed unsuitable for resection. The mortality was as high in patients where intubation was carried out as a definitive primary procedure as in those where it was performed when resection was found impossible. A review of the literature confirms that any impression that intubation is a procedure accompanied by relatively low mortality is incorrect (Waddington and Bickford, 1961; Collis, 1971).

The reduction in the average number of days spent in hospital by those patients surviving after a resection operation or intubation from 27–30 days in the 1961–5 period to 16–19 days in the 1971–5 period is encouraging and brings a small ray of light to otherwise depressing results. It suggests that pre- and postoperative care have, in fact, improved during the 15 years covered by the study, but it does make the absence of improvement of the hospital mortality particularly disappointing. One would like to believe that with improved perioperative care, the mortality associated with oesophagectomy could be further reduced. A careful study of the percentage of patients undergoing operation, their age range and average age, the duration of their symptoms and the extent of the disease at the time of [illegible] to show any significant difference bet[illegible]d in the first 5-year period and those in e[illegible] two later 5-year periods; it therefore cannot be confirmed that the patients being selected for resection were less fit in the later periods than in the earlier, although it is possible that this still may be the case.

Although the numbers involved are [illegible]tively small, there is a greater risk of dying as a resu[illegible] resection operation if significant concurrent disease is present. The risk would appear to be less in upper partial gastrectomy than in two-stage oesophagectomy or Roux loop procedures, and possibly can be explained by the fact that upper partial gastrectomy is frequently a rather quicker and less stressful operation. In patients with existing pulmonary or cardiac disease it would therefore seem that, whenever possible, an upper partial gastrectomy might be preferred to a Roux loop procedure.

In the present series 5 hospital deaths were associated with anastomotic leaks and there were a further 3 non-fatal leaks (overall incidence of 3·7 per cent). This very low incidence of leakage at the site of anastomosis almost certainly resulted from the meticulous attention paid to this part of the procedure, both with regard to the maintenance of viability of the tissues and to the technique of anastomosis.

The two-layered technique, involving a relatively large number of interrupted linen-thread sutures, resulted in inversion of the tissues at the site of anastomosis and this may have been a factor in the moderately high incidence of patients requiring dilatation for benign stricture formation at some stage during the first few weeks after operation. Few patients, however, required dilatation on more than one occasion, and this complication was rarely a major problem.

The results of long term follow-up make depressing reading, with a 1-year mortality of 46 per cent even in those patients surviving resection. By 2 years 75 per cent of the patients who underwent successful resection were dead and by 5 years approximately 86 per cent had died.

Comparison of long term results is difficult as many reported series differ in important details and are not always strictly comparable, but the 5-year survival rate of 14 per cent following successful resection falls within the average of most published series, where survival rates of 3·8 to 23·5 per cent have been reported (Collis, 1971; McKeown, 1974). The 23·5 per cent 5-year survival obtained by McKeown (1974) is exceptional. Similarly, the 1- and 2-year survival figures of 54 and 25 per cent achieved in the present series are average for this disease (McKeown, 1974).

There appears to be little difference in the prognosis between those patients presenting with tumours of the middle third of the oesophagus and those presenting with tumours of the lower third and cardia. The percentage survival at 1, 2 and 5 years showed little difference and the overall average survival in months is again similar, although in both cases slightly better results were obtained with middle third tumours. However, the outlook is bleak with tumours at either site.

The various merits of upper partial gastrectomy with direct oesophagogastric anastomosis and total gastrectomy with Roux-en-Y jejunal replacement have been discussed fully by McKeown (1973). Total gastrectomy allows fuller block dissection of the regional lymph nodes, yet the preservation of the pyloric antrum for oesophagogastric anastomosis is more physiological and is surely an advantage if the long term survival of the patient were not adversely affected which, unfortunately, was not the case in the present series where there was a significant difference in the average length of survival in months following resection by upper partial gastrectomy when compared with the Roux loop procedure in those patients where there was no identifiable lymph node involvement or secondary deposits. Average survival was 12 months longer following a Roux loop procedure when the tumour had not spread locally and 20 months longer when local spread had occurred but regional lymph nodes remained uninvolved. This extended survival is very considerable when put in the context of the usual outcome of the disease and the overall results in this series.

The improved survival following Roux loop procedures in this small group of patients (37 patients in all—16 Roux and 21 upper partial gastrectomies) may be explained in a number of ways. Upper partial gastrectomy, being an operation that takes rather less time than a Roux loop procedure, may have been chosen in particularly elderly or debilitated patients in whom a reduction in operating time was preferable; this has not been the case in this series. As upper partial gastrectomy was performed only in those patients with tumours of the lower third of the oesophagus and not in those having involvement of the cardia and lesser curves, it could be assumed that lower third tumours must have a poorer prognosis than tumours of the cardia; this assumption is not generally accepted as being true and, in fact, the reverse is usually considered to be the case (McKeown, 1974). The most likely explanation of this improvement of survival is that a Roux loop procedure, involving the removal of a larger area of tissue and a larger number of the regional lymph nodes, is a more radical and therefore a more preferable cancer operation for tumours of this region.

The extremely short survival with an average of less than 3 months for patients managed by intubation and other methods of therapy illustrates the advanced nature of their disease and correlates well with other reports (Miller, 1961; Amman and Collis, 1971).

The poor average survival of between 3·5 and 5 months obtained in those patients with secondary deposits at the time of resection is little improvement on the survival rate following intubation, and this must make resection of questionable value in this group of patients, particularly if the tumour is sited at the lower end of the oesophagus or cardia. Resection undoubtedly led to a few weeks' improvement in swallowing, but when the morbidity and debility associated with such a major operation are considered, the effort by both patient and surgeon would hardly seem worth while. Possibly some form of bypass operation should be considered in these cases.

Acknowledgement

The authors wish to thank Mrs B. Westbrook for considerable secretarial assistance.

References

AMMAN J. F. and COLLIS J. L. (1971) Palliative intubation of the oesophagus. *J. Thorac. Cardiovasc. Surg.* **61**, 863–869.

GOLLIS J. L. (1971) Surgical treatment of carcinoma of the oesophagus and cardia. *Br. J. Surg.* **58**, 801–804.

LEVERMENT J. N. and MILNE D. M. (1974) Oesophagogastrectomy in the treatment of malignancy of the thoracic oesophagus and cardia. *Br. J. Surg.* **61**, 683–688.

MCKEOWN K. C. (1972) Trends in oesophageal resection for carcinoma. *Ann. R. Coll. Surg. Engl.* **51**, 213–238.

MCKEOWN K. C. (1973) Carcinoma of the oesophagus. In: TAYLOR S. (ed.) *Recent Advances in Surgery*, 8. Edinburgh, Churchill Livingstone, [illegible]

MCKEOWN K. C. (1974) The [illegible] ment of carcinoma of the oesophagus. *Proc* [illegible] *Med.* **67**, 389–395.

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MI [illegible]

REGIS [illegible] *Review* [illegible] HMS [illegible]

WADE [illegible] (1961 [illegible] e for palliation in [illegible] cardia. *Br. J. Surg.* **49**, 5

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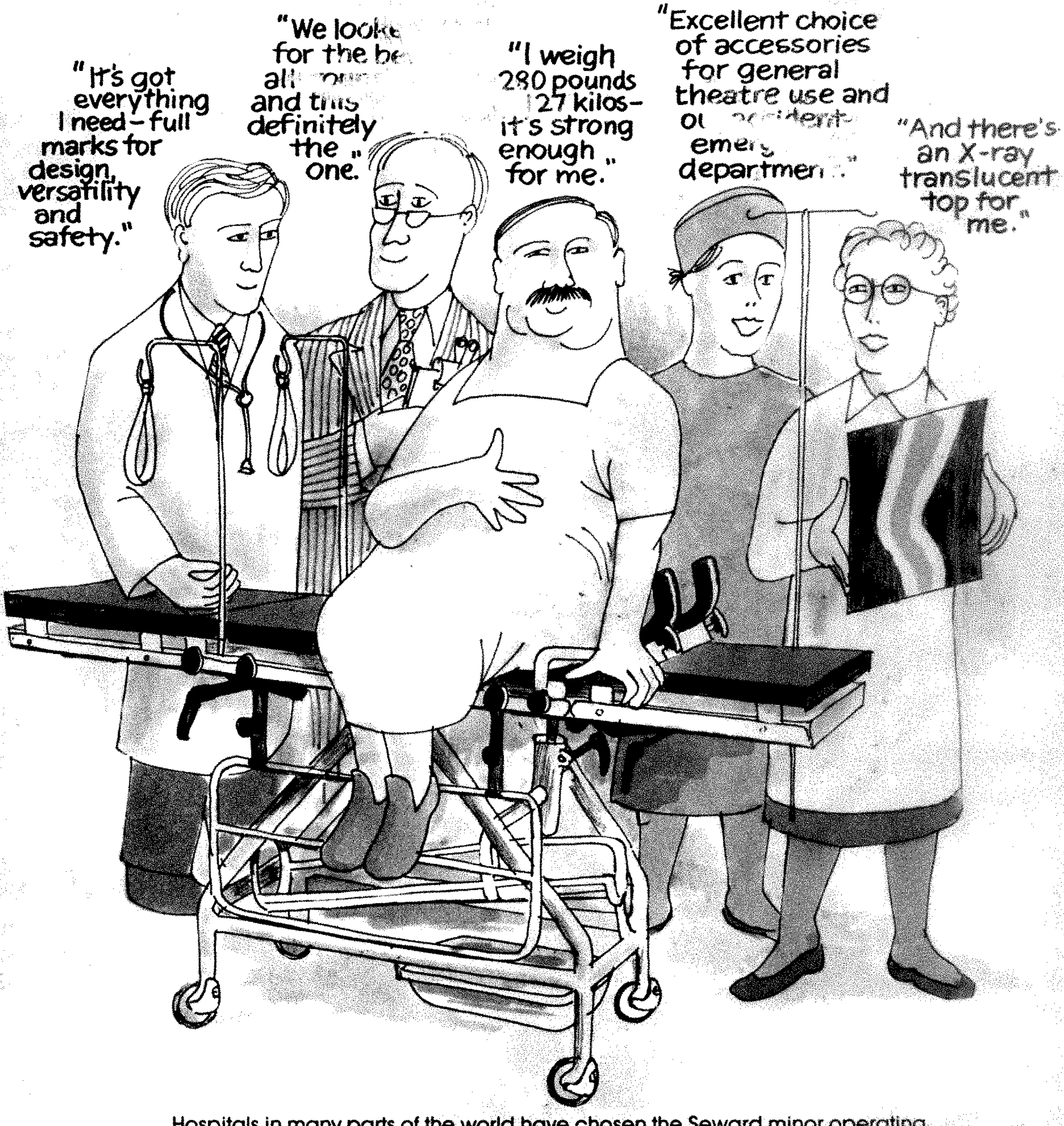
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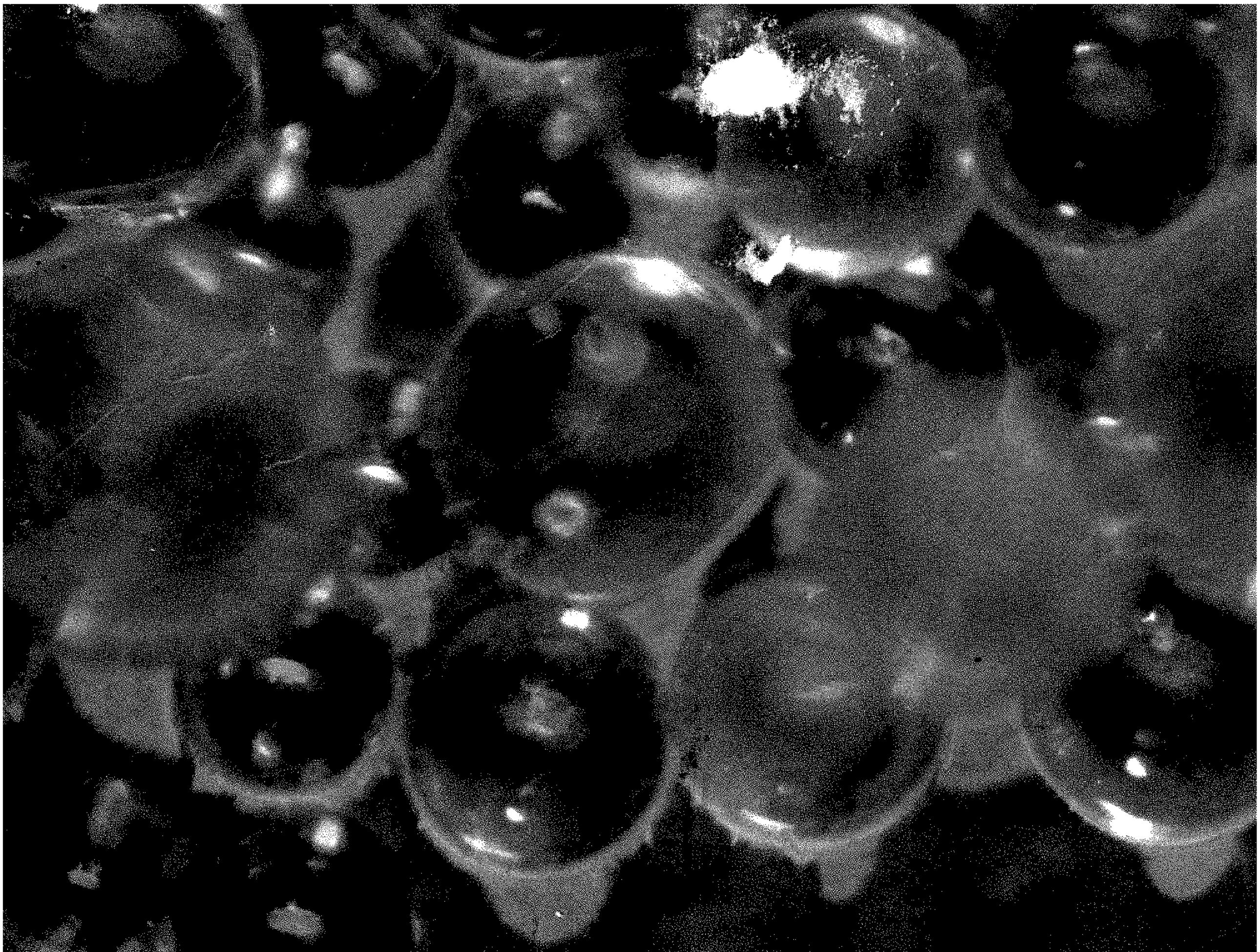

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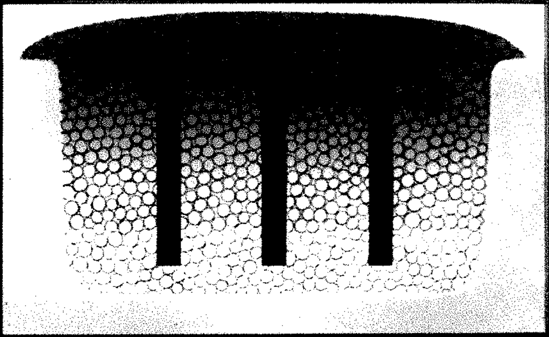

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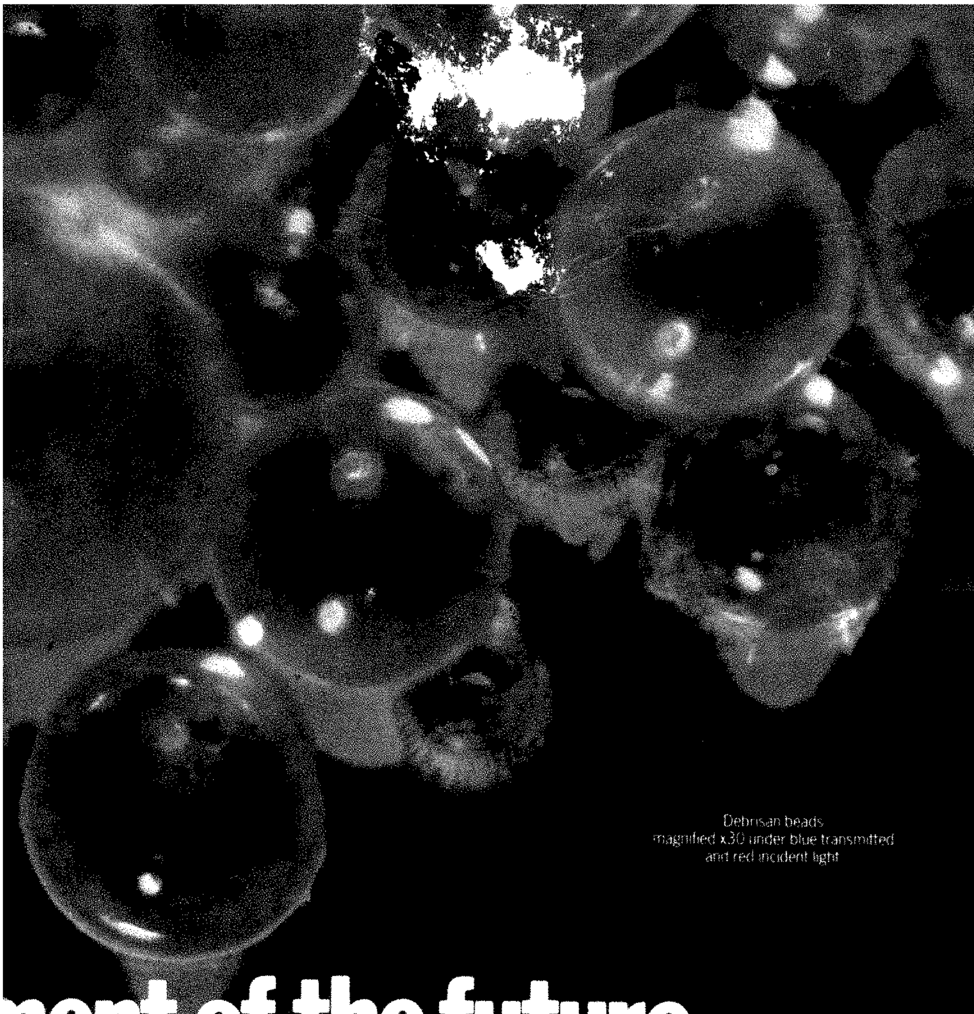

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4) No side-effects have been reported.

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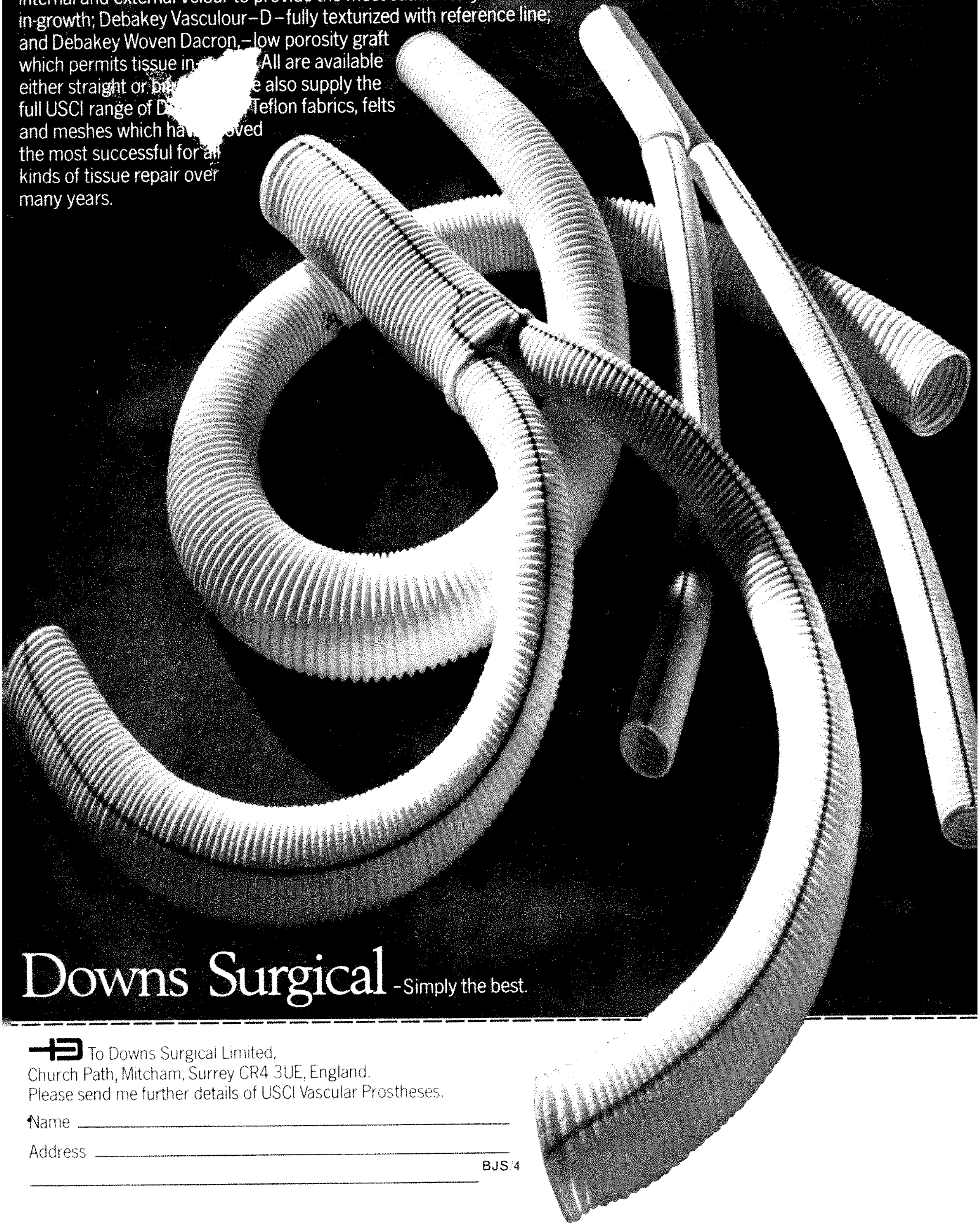

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Chylothorax following resection of the oesophagus

K. H. LAM, S. T. K. LIM, JOHN WONG AND G. B. ONG*

SUMMARY

Chylothorax complicating operations on the oesophagus has been reported infrequently; it carries a mortality rate of about 50 per cent. A search of the literature has yielded only 10 cases. This paper reports 4 further cases which occurred among 685 resections of the oesophagus, giving an incidence of 0·6 per cent. The diagnosis should be confirmed with lymphangiography. Treatment should be early exploration and ligation in patients in whom the thoracic duct has been divided at operation. If the duct has been injured during blind dissection a period of conservative treatment is advisable. Parenteral nutrition is a useful adjunctive treatment.

SINCE its description by Bartolet in 1633 chylothorax has been reported as a complication of a large variety of operations. The incidence has risen in the past two decades because of the increase in the number of thoracic operations, and trauma from road accidents. Furthermore, increased awareness of the condition is also likely to contribute to the growing number of reports of this condition.

Although operations on the oesophagus have now been carried out for 60 years, it is surprising to note the low incidence of chylothorax resulting from damage to the thoracic duct. A search of the literature revealed only 10 cases. It is the purpose of this paper to review the literature, report 4 additional cases and discuss the problem of chylothorax in relation to operations on the oesophagus.

Review of the literature

Bressler et al. (1953) were the first to report chylothorax complicating oesophageal surgery (*Table I*). Their patient underwent oesophagectomy for carcinoma of the middle third through a left thoracotomy. The chylothorax which complicated the operation was treated with closed chest drainage and the patient survived. Since then there have been only 5 other reports of chylothorax following oesophageal resection (Brewer, 1955; Williams and Burford, 1964; Gingell, 1965; Roy et al., 1967; Rubin et al., 1977), and one reported series of 152 cases of carcinoma of oesophagus in which chylothorax was reported as a complication (Wu et al., 1955). Altogether 10 cases of chylothorax complicating oesophageal operations were collected from the literature. In only 8 cases was the method of treatment reported, and this included repeated aspiration in 2, chest drainage in 3, iodized talc insufflation in 1 and exploration with ligation of the duct in 2. The outcome of the patients was mentioned in 9 cases—3 succumbed and 6 survived.

Case reports

Since 1966 we have encountered 4 cases of chylothorax developing following oesophagectomy. Three of these cases were squamous cell carcinoma of the oesophagus, 2 at the middle third and 1 at the upper third. Oesophagectomy was performed in these patients. The fourth case was a squamous cell carcinoma of the piriform fossa for which pharyngolaryngo-oesophagectomy was [illegible]formed.

Between the years 1966 a[illegible]7 inclusive, 580 resections of the oesophagu[illegible]cinoma were performed and 105 pharyn[illegible]-oesophagectomies for cancer of the hyp[illegible]ynx or larynx. Therefore, the incidence of chylothorax complicating resection of cancer of the oesophagus was 0·5 per cent and that complicating pharyngolaryngo-oesophagectomy was 0·9 per cent. Altogether for all types of resection, the incidence was 0·6 per cent.

Case 1: B. S. M., a male aged 60, was admitted with a 3-month history of dysphagia. Investigations demonstrated a squamous cell carcinoma of the middle third of the oesophagus. As the patient could not swallow and was emaciated a feeding gastrostomy was created. Three weeks later oesophagectomy was performed through a right thoracotomy approach and, as postoperative radiotherapy was planned, no reconstruction was carried out at this stage. A segment of the thoracic duct adjacent to the tumour was resected (which was our usual practice) and the ends ligated with thread. The cervical oesophagus was brought out as an oesophagostome. The cardia of the stomach was closed with catgut and returned to the abdomen. For the first 5 days after the operation the patient was well and gastrostomy feeding with liquidized food was resumed. On day 6 a sudden gush of milky fluid issued from the right chest drain. A chylothorax was suspected and the presence of fat in the fluid was demonstrated with Sudan III stain. Exploration was performed through the previous right thoracotomy incision. Liquidized food was found leaking from the cardiac end of the stomach into the chest. The chest was closed and the abdomen opened. The cardia was trimmed and then closed with two layers of catgut suture. The amount of fluid draining from the right chest decreased for a few days but up to 1000 ml of milky fluid was again collected each day. The drainage fluid was again positive with Sudan III stain. Re-exploration was carried out through the right chest and extensive adhesions were found. The defect of the thoracic duct was identified alongside the azygos vein and was transfixed. There was extensive oozing from the raw surfaces and the patient went into shock postoperatively. Resuscitation was unsuccessful and the patient died 3 days later.

Case 2: L. H., a male aged 66, was admitted to our unit with carcinoma of the middle of the thoracic oesophagus. A Lewis–Tanner operation was performed. As in *Case* 1, a segment of thoracic duct was resected. Postoperatively the chest drain persistently yielded a large amount of milky fluid, up to 2000 ml per day. Chylothorax was confirmed when analysis of the fluid for total lipids showed that the level rose from 2·9 to 4·5 g/l in 2½ h after ingestion of 100 g of cream. Re-exploration was performed on day 6 and the site of chyle leakage identified and ligated. Although the amount of fluid draining from the right chest decreased, it had become purulent, and *Pseudomonas aeruginosa* was cultured from the fluid. The condition of the patient deteriorated and he died 8 days later.

Case 3: K. Y., a male aged 52, was admitted with hoarseness of voice and dysphagia. Endoscopy revealed a tumour arising from the right piriform fossa, extending into the larynx. Preoperative radiotherapy was given. Pharyngolaryngo-oesophagectomy was performed, during which the oesophagus was moblized blindly with the hand through an enlarged oesophageal

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Table 1: REPORTED CASES OF CHYLOTHORAX AFTER OESOPHAGEAL SURGERY

Author	No. of cases	No. in series of chylothorax	No. in series of operation	Nature of pathology	Operation		Treatment	Outcome
Bressler et al. (1953)	1	1	—	Mid 1/3 carcinoma	Oesophagectomy, L thoracotomy		None	Survived
Brewer (1955)	2	24	—	Carcinoma	Oesoph[illegible]	[illegible]ed aspiration	1 ligation	1 survived (ligation), 1 died (aspiration alone)
Wu et al. (1955)	2	—	152	Mid 1/3 carcinoma	Oesophagectomy	Chest drainage, 50% glucose instillation	None	1 survived, 1 died
Williams and Burford (1964)	1	11	—	Unresectable carcinoma	? Nature	? Nature	None	Died
Gingell (1965)	1	3	—	Lower 1/3 carcinoma	Oesophagectomy, L thoracotomy	Iodized talc insufflation	None	Survived
Roy et al. (1967)	1	52	—	Carcinoma	Oesophagectomy	?	?	?
Rubin et al. (1977)	2	14	—	?	Oesophagectomy	1 thoracocentesis	1 ligation	2 survived
Present series (1979)	4	—	685	Carcinoma of oesophagus: 1 upper 1/3, 2 mid 1/3, 1 carcinoma of piriform fossa	1 oesophagectomy, split sternum; 2 oesophagectomy, R thoracotomy; 1 pharyngolaryngo-oesophagectomy	1 chest drainage + parenteral nutrition	3 ligation	1 survived, 3 died

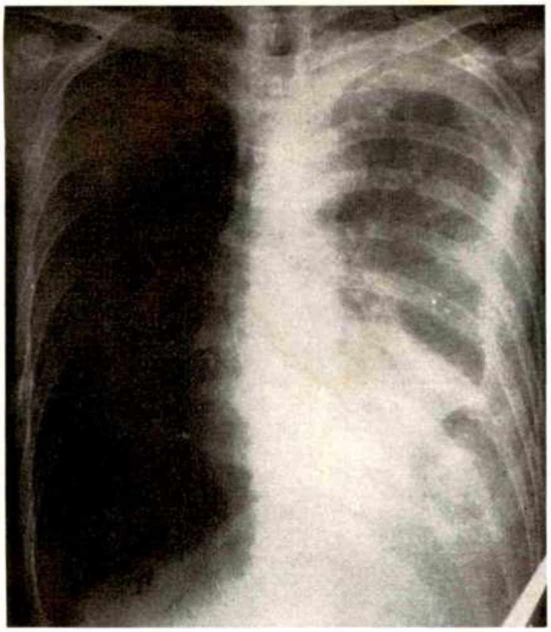


Fig. 1. *Case* 3. Chest X-ray showing left chylous effusion.

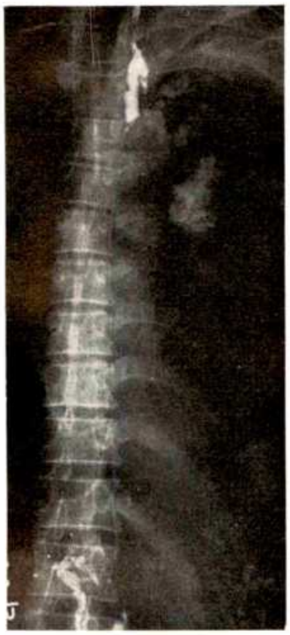
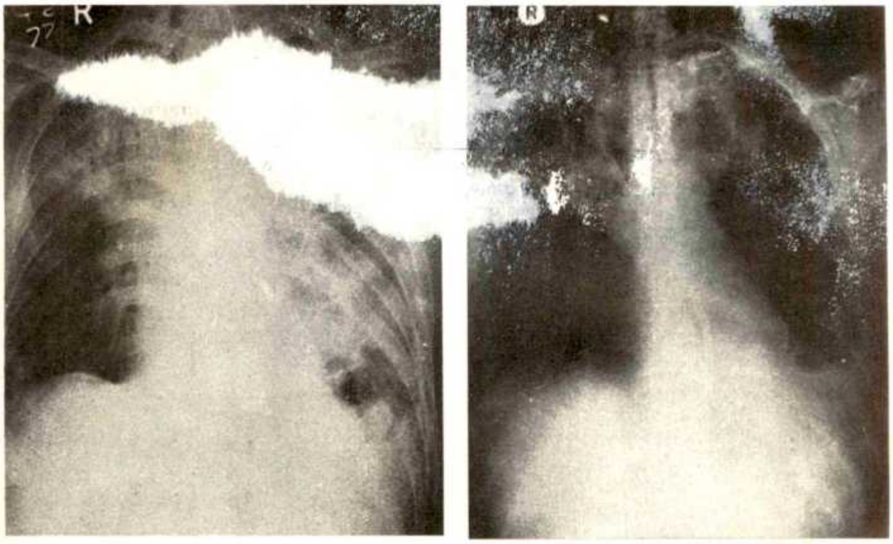


Fig. 2. *Case* 3. Lymphangiogram showing leakage of thoracic duct.

hiatus of the diaphragm. The mediastinal pleurae of both sides were opened during blind dissection and therefore chest drains were inserted. Postoperatively there was persistent drainage of more than 1000 ml of milky fluid from the left chest drain each day and chest X-ray showed persistent left pleural effusion (*Fig.* 1). Chylothorax was suspected and lymphangiography was performed (*Fig.* 2). Leakage from the upper segment of thoracic duct was demonstrated. As the drainage did not subside, on day 10 a right thoracotomy was performed and the thoracic duct identified and ligated. The chylous leakage was controlled. However, the patient developed bronchopneumonia and pulmonary oedema, resulting in death 1 week later.

Case 4: L. K. T., a male aged 57, was admitted with a 4-month history of dysphagia. Investigation showed a poorly differentiated squamous carcinoma of the oesophagus, at a level of 20 cm from the upper incisor teeth.



a *b*

Fig. 3. *Case* 4. Serial chest X-rays showing development of chylous collection. *a*, Day 5, mediastinal shadow well formed in the upper mediastinum. *b*, Day 6, mediastinal shadow decreasing in size after discharge of chyle.

A course of preoperative radiotherapy was given. Subsequently oesophagectomy was performed using the split sternum approach. The tumour-bearing part of the oesophagus was approached above the aortic arch, while the distal segment was freed by blind blunt dissection. For reconstruction the mobilized stomach was delivered to the neck through the posterior mediastinum and anastomosed to the cervical oesophagus. Postoperatively the patient was well. Only small amounts of fluid were drained from the chest. Daily chest X-ray showed a large opacity appearing gradually at the superior mediastinum (*Fig.* 3). This was subsequently shown to be a collection of chyle.

On the fifth postoperative day serous fluid discharged from the neck wound, and on the next day 1 litre of milky pleural fluid discharged from the left chest drain. Test with Sudan III stain showed the presence of lipid. A chylothorax was suspected. Lymphangiography was performed, confirming that the thoracic duct was draining into this collection of chyle at the superior mediastinum (*Fig.* 4). Parenteral nutrition was commenced because the excessive chest drainage amounted to 1000–2000 ml per day. Seven days after the onset of chylothorax the drainage gradually decreased. A repeat lymphangiogram showed no further extravasation. Parenteral feeding was maintained for another week before oral feeding was commenced. Apart from an infected sternal wound there was no other complication. The patient was discharged well after 3 months.

Discussion

The thoracic duct is in close relation with the oesophagus along most of its course, particularly in the thorax. It crosses from the right to the left side at the 5th or 6th thoracic vertebra (Van Pernis, 1949). Thus, when the lower thoracic segment is injured, chyle leaks into the right pleural cavity, whereas when the upper segment is damaged a chylothorax occurs on the left side (Ross, 1961). For carcinoma of the middle oesophagus our usual approach for oesophagectomy is through the right chest. A segment of thoracic duct near the tumour was routinely removed and the divided ends ligated with non-absorbable sutures. In *Cases* 1 and 2 the chylothorax probably resulted from slipping of the lower ligatures so that chyle drained into the right chest. During pharyngolaryngo-oesophagectomy for carcinoma of the piriform fossa (*Case* 3) and oesophagectomy via the split sternum approach (*Case* 4) the whole or part of the oesophagus was dissected blindly. Considering the proximity of the thoracic duct to the oesophagus and the frailness

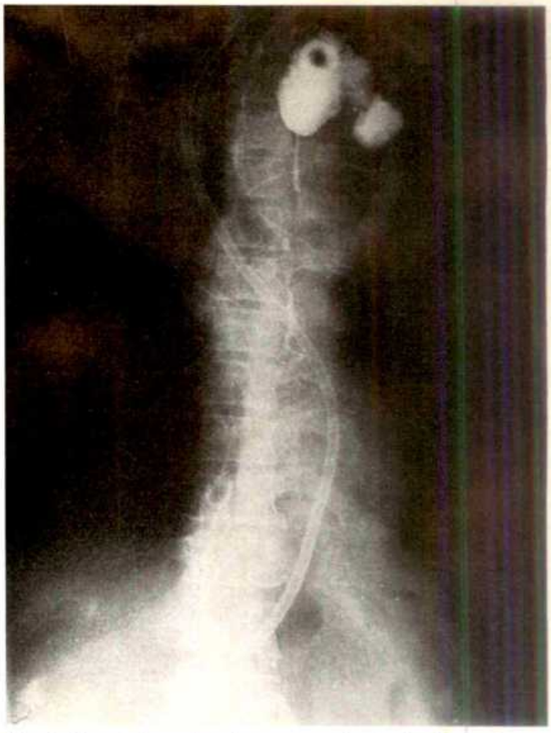


Fig. 4. *Case* 4. Lymphangiogram confirming leakage of thoracic duct into mediastinum.

of this and other nearby lymphatic channels it is surprising that chylothorax did not occur more often. In both these cases the upper part of the thoracic duct was damaged, thereby resulting in left-sided chylothorax.

Diagnosis of chylothorax is usually suspected when a large milky pleural effusion d[illegible] support for, but not confirmation of, [illegible] may be obtained with the detection [illegible] the fluid, or a characteristic [illegible] (Seriff et al., 1977), or the prese[illegible] in pleural fluid when fed orally (K[illegible] and Berry, 1954; Kjeldsen and Struve-Christensen, 1974). Roy et al. (1967) have emphasized that not all milky effusions are sequelae of thoracic duct fistulas. We also agree that these tests alone are not adequate for diagnosis of chylothorax, especially in patients who have undergone oesophagectomy, because of the complexity of the operative procedures involving various parts of the gastrointestinal tract. This is illustrated by *Case* 1, in whom fat-containing liquidized food leaked from the stomach. In another case of carcinoma of the oesophagus which we encountered, lipid-laden discharge issued via the right chest drain after oesophagectomy and stomach reconstruction. The diagnosis of chylothorax was shown to be erroneous when, at exploration, the thoracic duct was found to be intact and leakage from a perforated pyloromyotomy site was demonstrated. In both these cases, standard tests for lipid in the pleural fluid will be positive and any contrast medium given orally or by way of a nasogastric tube will also be recoverable through the chest drain.

Thus confirmation of the diagnosis of chylothorax complicating oesophageal surgery should be obtained by lymphangiography, the use of which has previously been described (Heilman and Collins, 1963; Nusbaum et al., 1964; Chavez and Conn, 1966; Carniel et al., 1971; Diaconis et al., 1976). This was performed in *Cases* 3 and 4. Lymphangiography not only established the diagnosis, but the site and degree of extravasation were also demonstrable. In addition, repeating the investigation allowed assessment of the progress and assisted in the decision to persevere with conservative treatment (*Case* 4).

The presence of a latent period before appearance of chylous pleural effusion (Garamella, 1958; Steiger et al., 1960; Ross, 1961; Tandon, 1968; Higgins and Mulder, 1971) is illustrated in *Case* 4. The delay is because of intact mediastinal pleurae holding the chyle in the mediastinum for the initial 3–5 days. On occasions when the amount of chyle is great it gives rise to a large mediastinal shadow before finally rupturing into the pleural cavity. Such an occurrence was mentioned by Bressler et al. (1953) and by Thorne (1958) and emphasized by Higgins and Mulder (1970). However, no chylous collection will develop if the mediastinal pleura has been damaged during operation, as in oesophagectomy via a thoracotomy incision (*Cases* 1 and 2), or if the pleura has been torn during blind dissection of the oesophagus (*Case* 3).

Goorwitch (1955) has presented a comprehensive review of the trend of treatment of chylothorax from a variety of causes. In 1948 Lampson reported the first successful case of transthoracic ligation of the thoracic duct. Before that time the treatment of chylothorax consisted of thoracocentesis, catheter drainage, rib resection, cervical ligation and phrenic nerve crushing, with a mortality rate of 45 per cent. Since Lampson's review, Goorwitch had collected 31 cases, of which 15 were treated with ligation of the duct with no mortality. He concluded that when chylothorax persisted despite adequate thoracocentesis or closed drainage, the thoracic duct should be ligated before the condition of the patient began to deteriorate. Later reports, however, have advocated non-operative treatment. Schmidt (1959) advised conservative therapy because of better prognosis; Maloney and Spencer (1956) advised trial of conservative measures for at least 3–4 weeks before considering surgery; Williams and Burford (1964) concluded that surgical intervention is rarely indicated; Selle et al. (1971) reviewed the indications for surgery in chylothorax and recommended ligation of the thoracic duct when there is daily loss of more than 1500 ml and when this is likely to last more than 14 days.

When chylothorax results from operations on the oesophagus we agree with the principle advanced by Selle et al. (1971). However, the mechanism of injury has to be taken into account in the selection of cases for operative or conservative treatment. The success of conservative treatment depends on collateral channels opening up, as demonstrated clearly by Chavez and Conn in dogs (1966). When oesophagectomy is performed for middle or lower third tumour through a right or left thoracotomy, the whole posterior mediastinum is usually dissected clean (*Cases* 1 and 2), so that it is unlikely that sufficient collaterals are left behind to provide drainage of abdominal chyle. A much longer time is needed before more distant channels will open up. Therefore, early operative intervention with religation of the duct should be the treatment of choice. On the other hand, when the oesophagus is mobilized by transabdominal finger dissection close to its wall, adequate collateral lymphatic channels are probably still present which may open up readily. In these cases it is worth while to attempt conservative treatment for a period, if the condition of the patient permits, before resorting to operative intervention. In *Cases* 3 and 4, the thoracic duct was damaged in this manner. *Case* 3 required ligation of the duct when drainage alone failed and *Case* 4 recovered with intercostal drainage alone.

Various other methods have been described for the treatment of chylothorax. Of interest is the method of induction of pleurodesis with iodized talc (Gingell, 1965). Among the three successfully treated cases reported by Gingell (1965), one patient had developed chylothorax following oesophagectomy for carcinoma of the lower third. This method may be employed if operation is contraindicated. Anastomosis of the thoracic duct to the azygos or hemiazygos vein (Brewer, 1955) seems unnecessarily complicated when ligation would suffice.

Identification at exploration of the site of chylous leakage usually presents no difficulty. However, many methods have been described which assist localization of the site of injury of the duct. These included preoperative administration of cream (Schmidt 1959), nasogastric instillation of methylene blue at operation (Engevik, 1976), subcutaneous injection of normal saline to increase the flow of chyle (Steiger et al., 1960), subcutaneous injection of Evans blue (Merrill, 1955) and filling the thorax with saline during operation to facilitate detection of milky chyle (Elliot, 1954). These may be attempted if difficulty is encountered at exploration.

A useful adjunct in the conservative management of patients with chylothorax is the use of medium chain triglycerides (Lichter et al., 1968; Tamir et al., 1968). The flow of chyle along the thoracic duct can be decreased since these triglycerides are absorbed directly into the bloodstream and do not enter the lymphatic system (Hashim et al., 1964). It is more effective to stop oral feeding completely and commence total parenteral nutrition (Birt and Connolly, 1952). The use of this method undoubtedly contributed to the success of *Case* 4 reported in this paper.

The mortality of chylothorax complicating oesophageal operations is high (*Table I*). Altogether 6 cases out of 13 with known outcome have died, giving a mortality rate of about 50 per cent. The high rate probably represents complications superadded to an operation which itself carries a mortality rate of 20–30 per cent.

References

BALDRIDGE R. R. and LEWIS R. V. (1948) Traumatic chylothorax. *Ann. Surg.* **128**, 1056–1078.

BARTOLET X. X. (1633) Cited by BOWER (1964).

BIRT A B. and CONNOLLY N. Y. (1952) Traumatic chylothorax. A report of a case and a survey of the literature. *Br. J. Surg.* **39**, 564–568.

BOWER G. C. (1964) Chylothorax: observations in 20 cases. *Dis. Chest* **46**, 464–468.

BRESSLER S., WIENER D. and THOMPSON S. A. (1953) Traumatic chylothorax following oesophageal resection. *J. Thorac. Surg.* **26**, 321–324.

BREWER L. A. (1955) Surgical management of lesions of the thoracic duct. The technic and indications for retroperitoneal anastomosis of the thoracic duct to the hemiazygos vein. *Am. J. Surg.* **90**, 210–227.

CARNIEL M. R., BENNINGHOFF D. L. and ALEXANDER L. L. (1971) Chylous effusions, extravasating lymphographic contrast material, hypoplasia of lymph nodes and lymphocytopenia. *Chest* **59**, 107–110.

CHAVEZ C. M. and CONN J. H. (1966) Thoracic duct laceration. Closure under conservative management based on lymphangiography evaluation. *J. Thorac. Cardiovasc. Surg.* **51**, 724–728.

DECANCQ H. G. jun. (1965) The treatment of chylothorax in children. *Surg. Gynecol. Obstet.* **121**, 509–512.

DIACONIS J. N., WEINER C. I. and WHITE D. W. (1976) Primary subclavian vein thrombosis and bilateral chylothorax documented by lymphography and venography. *Radiology* **118**, 557–558.

ELLIOT A. W. (1954) Traumatic chylothorax. *Can. Med. Assoc. J.* **70**, 71–72.

ENGEVIK L. (1976) Traumatic chylothorax. *Scand. J. Thorac. Cardiovasc. Surg.* **10**, 77–78.

GARAMELLA J. J. (1958) Chylothorax treated by ligation of thoracic duct and studies in thoracic ductography. *Arch. Surg.* **76**, 46–53.

GINGELL J. C. (1965) Treatment of chylothorax by producing pleurodesis using iodized talc. *Thorax* **20**, 261–269.

GOORWITCH J. (19[illegible]) Traumatic chylothorax and thoracic duct ligation[illegible] *Thorac. Surg.* **29**, 467–479.

HASHIM [illegible] H. B., BABAYAN V. K. et al. (1964) Treat[illegible] and chylothorax with medium-chain [illegible] *N. Engl. J. Med.* **270**, 756–761.

HEILMAN R. D. and COLLINS V. P. (1963) Identification of laceration of the thoracic duct by lymphangiography. *Radiolo*[illegible] 72.

HIGGINS C[illegible] G. (1970) Mediastinal chyloma, a roentg[illegible] of chylous fistula. *JAMA* **211**, 1188.

HIGGINS C. B.[illegible]R D. G. (1971) Chylothorax after surgery for congenital heart disease. *J. Thorac. Cardiovasc. Surg.* **61**, [illegible]–418.

KJELDSEN C. S. and STRUVE-CHRISTENSEN E. (1974) Chylothorax. A case report. *Scand. J. Thorac. Cardiovasc. Surg.* **8**, 138–141.

KLEPSER R. G. and BERRY J. F. (1954) The diagnosis and surgical management of chylothorax with the aid of lipophilic dyes. *Dis. Chest* **25**, 409–426.

LAMPSON R. S. (1948) Traumatic chylothorax. *J. Thorac. Surg.* **17**, 778–791.

LICHTER I., HILL G. L. and NYE E. R. (1968) The use of medium-chain triglyceride in the treatment of chylothorax in a child. *Ann. Thorac. Surg.* **5**, 352–355.

MALONEY J. V. jun. and SPENCER F. C. (1956) The non-operative treatment of traumatic chylothorax. *Surgery* **40**, 121–128.

MERRILL K. (1955) The use of Evans blue to outline the course of the thoracic duct. *J. Thorac. Surg.* **29**, 555–557.

NUSBAUM M., BAUM S., HEDGES R. et al. (1964) Roentgenographic and direct visualisation of thoracic duct. *Arch. Surg.* **88**, 105–113.

ROSS J. K. (1961) A review of the surgery of the thoracic duct. *Thorax* **16**, 12–21.

ROY P. H., CAN D. T. and SPENCER PAYNE W. (1967) The problem of chylothorax. *Mayo Clinic. Proc.* **42**, 457–467.

RUBIN J. W., MOORE H. V. and ELLISON R. G. (1977) Chylothorax: therapeutic alternatives. *Am. Surg.* **43**, 292–297.

SCHMIDT A. (1959) Chylothorax. Review of 5 years' cases in the literature and report of a case. *Acta Chir. Scand.* **118**, 5–12.

SELLE J. G., SNYDER W. H. and SCHNEIBER J. T. (1971) Chylothorax: indications for surgery. *Ann. Surg.* **177**, 245–249.

SERIFF N. S., COHEN M. L., SAMUEL P. et al. (1977) Chylothorax: diagnosis by lipoprotein electrophoresis of serum and pleural fluid. *Thorax* **32**, 98–100.

STEIGER Z., WEINBERG M. and FELL E. H. (1960) Postoperative chylothorax. *Am. J. Surg.* **100**, 8–11.

TAMIR I., HUNTER J. O., FOSBROOKE A. S et al. (1968) Serum and chyle lipids during medium drain triglycerides feeding in a child with chylothorax. *Arch. Dis. Child.* **43**, 302–306.

TANDON R. K. (1968) Chylothorax after repair of ventricular septal defect. *J. Thorac. Cardiovasc. Surg.* **56**, 378–380.

THORNE P. S. (1958) Traumatic chylothorax. *Tubercle (Lond.)* **39**, 29–34.

VAN PERNIS P. A. (1949) Variations of the thoracic duct. *Surgery* **26**, 806–809.

WILLIAMS K. R. and BURFORD T. H. (1964) The management of chylothorax. *Ann. Surg.* **160**, 131–140.

WU Y. K., HOWE Y. L., HUANG K. C. et al. (1955) Surgical treatment of carcinoma of the oesophagus and cardia of the stomach. *Chinese Med. J.* **73**, 181–195.

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Complications associated with [illegible] e use of the Celestin tube for benign oesophageal obstruction

M. B. RANSON AND H. T. JOHN*

SUMMARY

Two cases are described [illegible] of a Celestin tube took place [illegible] lodged in a benign oesophageal stricture for 14 months. One patient presented with apparent acute pancreatitis and the other with a minor gastrointestinal bleed.

Case reports

Case 1: A 76-year-old female with a 6-month history of dysphagia and regurgitation was shown at barium swallow examination and oesophagoscopy to have an endoscopically impassable stricture at 25 cm which appeared benign and from which brushings and biopsies were negative for malignant cells. The barium swallow showed a large sliding hiatus hernia with oesophagogastric reflux. On physical examination, however, a lump in the right breast was discovered which proved to be a carcinoma. Subsequently, in March 1976, she had a right mastectomy and a Celestin tube (Celestin, 1959) was inserted in the oesophagus through a high gastrotomy (Das and John, 1973). A large lymph node at the hiatus was removed, and on histology this proved to be inflammatory.

At a follow-up visit 11 months later she complained of some dysphagia and was seen to have an incisional hernia. Barium swallow examination was repeated and showed a patent, correctly positioned tube but with a bolus of food above it. The patient was recommended to drink aerated fluids. Four months later she was admitted as an emergency complaining of epigastric pain and she had fainted following the passage of a small melaena stool. Oesophagoscopy showed that the upper end of the tube was at 25 cm and there was free regurgitation of gastric contents. However, a barium swallow examination showed that the tube was blocked distally and the barium was seen to trickle down the sides (*Fig.* 1). An abdominal radiograph taken at the same time showed a radio-opaque marker in the right iliac fossa (*Fig.* 2). At operation the upper part of the tube was first removed with the rigid oesophagoscope and then the lower part was extracted after opening the caecum at laparotomy. The nylon spiral joining the two was cut (*Fig.* 3, note the plum stone also seen within the tube in *Fig.* 1). Both the hiatus and incisional hernias were repaired and 3 months later the patient was well and gaining weight, with no dysphagia and a sound scar.

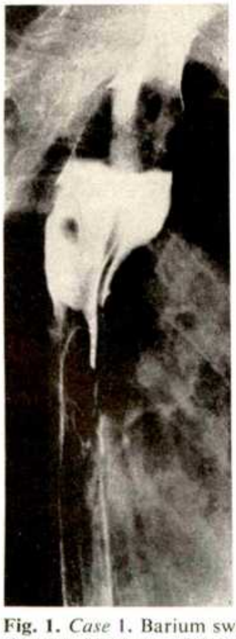

Fig. 1. *Case* 1. Barium swallow showing blockage of the Celestin tube in part by a plum stone

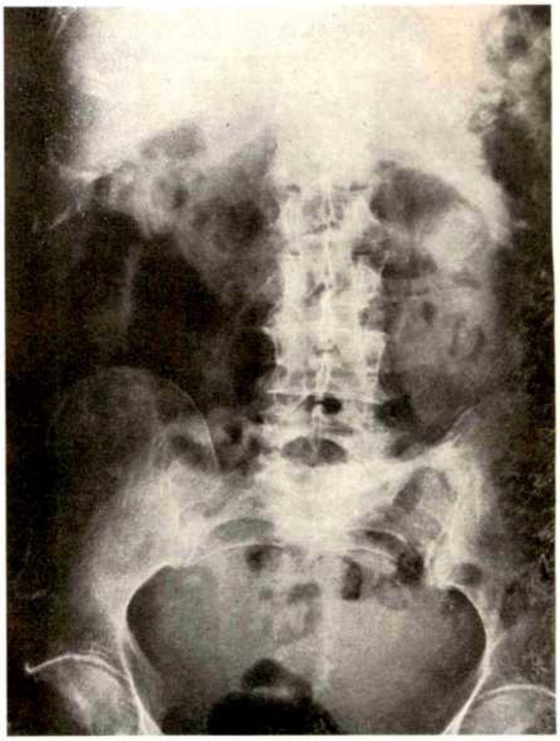

Fig. 2 *Case* 1. Abdominal radiograph showing the Celestin tube marker in the right iliac fossa.

Case 2: A 74-year-old female presented with a 3-year history of increasing weight loss and regurgitation of food. A barium swallow examination suggested late onset achalasia, but at oesophagoscopy a stricture was revealed at 40 cm from which brushings and biopsies were negative for malignant cells. Following the insertion of a Celestin tube the patient remained well, gaining weight until 14 months later, when she presented as an emergency with a 4-week history of intermittent, then constant abdominal pain, nausea and vomiting. She did not complain of dysphagia. On examination there was some abdominal tenderness and investigation showed her serum amylase to be 8000 i.u./l (normal range 70–300). An abdominal radiograph showed the radio-opaque marker of her Celestin tube to be in two pieces (*Fig.* 4). Two weeks later, after the acute episode had passed, a further radiograph (*Fig.* 5) showed the two pieces to have changed position. At operation, the

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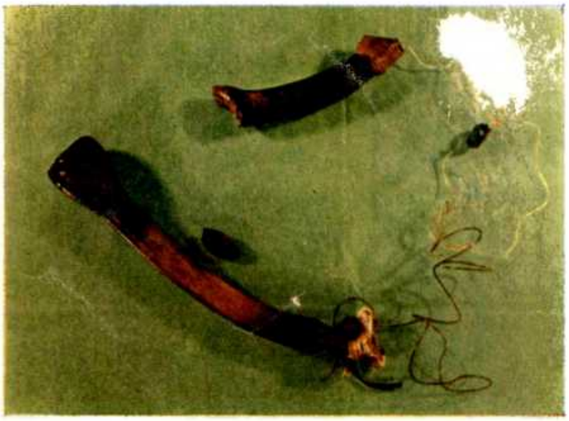

Fig. 3. *Case* 1. Celestin tube removed in two pieces with the plum stone that had blocked it.

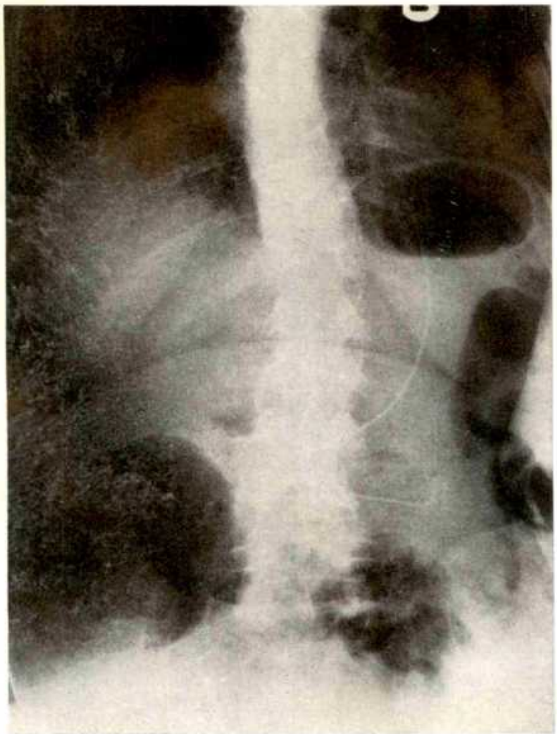

Fig. 4. *Case* 2. Abdominal radiograph showing the Celestin tube marker in two pieces.

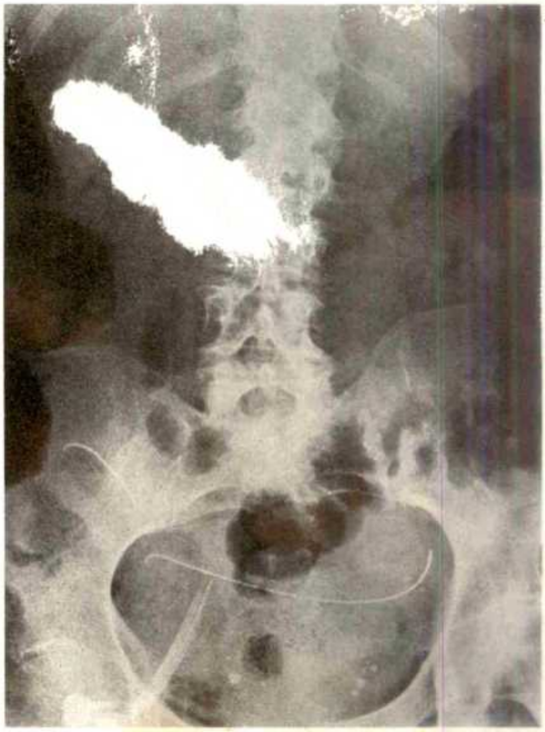

Fig. 5. *Case* 2. Change of position of the pieces of Celestin tube marker.

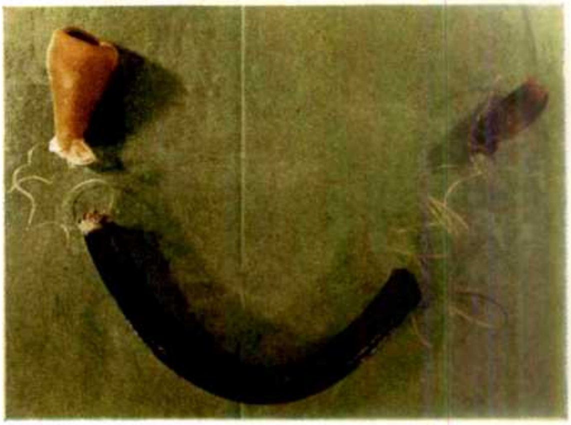

Fig. 6. *Case* 2. Celestin tube removed in three pieces.

funnel of the Celestin tube was at the oesophagogastric junction and the rest of the tube was in two pieces in the mid- and terminal ileum. There were dense adhesions of loops of ileum around the smaller piece suggesting that a perforation had occurred, perhaps accounting for the high serum amylase. The three pieces were attached to each other by two strands of nylon; all were removed (*Fig.* 6). The segment of ileum containing the lower portion of the tube was resected and the specimen showed histological evidence of a perforation. When seen 6 weeks later the patient was swallowing well with a sound scar.

Discussion

Structural deterioration of the nylon-latex Celestin tube when used in benign oesophageal stricture has been described previously (Mackenzie et al., 1976). These authors reported cases presenting with the complication at intervals of 2 and 3 years respectively. We, likewise, have not found the complication when the tube is used for palliation in neoplastic stricture, probably because in this group the remaining lifespan is short, few patients surviving as long as 14 months. On theoretical grounds at least the tube might be held rigidly in a lengthening adynamic tumour segment. With benign stricture constant movement may be responsible for the disintegration of the tube, for examination after removal shows the appearance of a fatigue fracture of the tube opposite the lower end of the stricture. It is suggested that where intubation for benign oesophageal stricture is considered in patients unfit or unsuitable for major procedures, the intubation should be temporary and the tube should be removed after an interval of 3–6 months and, if necessary, replaced at a later date.

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References

CELESTIN L. R. (1959) Permanent intubation in inoperable cancer of the oesophagus and cardia. *Ann. R. Coll. Surg. Engl.* **25**, 165–170.

DAS S. K. and JOHN H. T. (1973) Oesophageal intubation in obstructive lesions of the oesophagus. *Br. J. Surg.* **60**, 403–406.

MACKENZIE I., WHYTE A. S. and TANKEL H. I. (1976) Structural deterioration in Celestin tubes. *Br. J. Surg.* **63**, 851–852.

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Where should the frozen section be done?

There is no better stimulus to the production of confidence between pathologist and surgeon than the virtual presence of the unconscious patient. . . . Let me also say that no matter how much sophisticated apparatus contributes logistically to a pathology department, the corollary of a distant and perhaps unfamiliar pathologist has not further contributed to the speed or accuracy of diagnosis . . . .

McINTOSH D. (1978) Thyroid tumours. *J. R. Coll. Surg. Edinb.* **23**, 265–284.

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Translocating the aberrant right subclavian artery in dysphagia lusoria

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SUMMARY

A case of dysphagia lusoria with unusual associated symptoms in an adult is presented. The condition was treated by division of the aberrant right subclavian artery at its origin through a median sternotomy and translocating the distal subclavian artery to the aortic arch with an interposition Dacron graft. All the reported techniques of dividing and transposing the aberrant right subclavian artery in dysphagia lusoria are reviewed and discussed.

THE anomalous origin of the right subclavian artery has long been recognized. The first case was described by Hunauld in 1735. In 1789 Bayford reported a 62-year-old woman who died of extreme emaciation from oesophageal obstruction by an aberrant right subclavian artery. He coined the term 'dysphagia lusoria' to describe the condition. Kommerell described the radiological findings in 1936. In 1946 Gross first successfully relieved the dysphagia in a 4-month-old infant by dividing the aberrant artery through a left thoracotomy. Although the operation has since been performed and recorded on a number of occasions in infants, there had been no report of this operation for the relief of symptoms in adults until 1960 (Morris, 1960). Division of the anomalous right subclavian artery through a thoracotomy became the standard operation for dysphagia lusoria. No serious impairment of blood supply to the right arm was seen following division of the aberrant artery. Division of the subclavian artery is not without complications (Webb and Burford, 1952), however: in adults, development of the subclavian steal syndrome is a real possibility (Pifarre et al., 1971). The first report on re-establishing the continuity of the right subclavian artery after operation for dysphagia lusoria was described by Bailey et al. in 1965. Following this, four new procedures for the treatment of dysphagia lusoria were described in the literature (Siderys, 1969; Pifarre et al., 1971; Shumacker et al., 1971; Orvald et al., 1972). The purpose of this communication is to describe a case of dysphagia lusoria with unusual symptoms treated by a revised technique of translocating the aberrant artery and to review the various reported surgical techniques of dividing and reconstituting the aberrant right subclavian artery in the treatment of dysphagia lusoria.

Case report

The patient was a 46-year-old Chinese housewife. She complained of progressive difficulty over 8 months in swallowing hard food, associated with pain. There was no problem with fluid or soft diet. Hard and large pieces of food, such as apple, would 'get stuck' just behind the manubrium sterni and produce pain. In the recent 2 months she also experienced numbness of the left upper extremity. This was aggravated by lifting the left arm and carrying weights.

On examination, she was found to be in good general health. The carotid pulses were strong and equal. There was diminished *left* radial pulse. The blood pressure was 120/80 mmHg in the right arm and only 100/70 mmHg in the *left* arm. A grade 3/6 pansystolic murmur was heard all over the precordium with maximal intensity at the lower left sternal border. No other abnormalities were detected.

The chest radiograph and electrocardiogram were normal. A barium swallow examination (*Fig.* 1) revealed an indentation of the oesophagus at the level of D3, suggestive of external compression by an aberrant right subclavian artery. A transfemoral arch-aortogram (*Fig.* 2) confirmed the presence of an aberrant right subclavian artery. Since its origin was obscured by the overlying vessels, the presence or absence of a Kommerell's diverticulum (Kommerell, 1936) could not be determined by the arteriogram. Oesophagoscopy revealed nothing abnormal. A tentative diagnosis of dysphagia lusoria was made and the patient came to operation on 1 November 1977.

Through a median sternotomy incision the aortic arch and its four branches were exposed. The aberrant right subclavian artery was dissected out at the posterior mediastinum on both sides of the oesophagus and encircling tapes were applied. Kommerell's aneurysmal diverticulum was not observed (Kommerell, 1936). With gentle forward traction of the oesophagus, the retro-oesophageal portion of the artery was dissected from the right posterior mediastinum to its origin. Dissection from its origin upwards was difficult because of the presence of the left common carotid and left subclavian arteries. With one vascular clamp at the origin and another just proximal to the origin of the right vertebral artery, the aberrant right subclavian artery was transected to the left of the oesophagus. The proximal stump was oversewn. The retro-oesophageal portion of the right subclavian artery was brought to the right posterior mediastinum. It was then anastomosed to the aortic arch, end to side, proximal to the right common carotid artery, by means of an interposition Dacron graft and use of a partial exclusion clamp on the aorta (*Fig.* 3*b*). An interposition Dacron graft was used because the right subclavian artery was not long enough to anastomose directly to the aorta. The wound was closed in layers with four peristernal wires and a small mediastinal tubal drain.

Postoperatively, both radial pulses were palpable and equal. The blood pressure in both the upper extremities was 120/80 mmHg. The systolic murmur was found to be unchanged. Two days after the operation the patient volunteered the information that all her difficulty and pain in swallowing had completely disappeared and so had the numbness of her left upper extremity. She made a complete and uneventful recovery and was discharged well 14 days after the operation. A postoperative barium swallow examination revealed normal filling of the oesophagus with disappearance of the indentation (*Fig.* 4).

Discussion

The aberrant right subclavian artery is the most frequently encountered anomaly of the aortic arch. In the reported anatomical studies (Holzapfel, 1899; Goldbloom, 1922; Anson, 1936) its incidence varies from 0·6 to 1·8 per cent. Despite its common occurrence, clinical manifestations are unusual, and when they occur, they are usually noted in the first 2 or 3 years of life.

The arteria lusoria usually arises from the aorta posteriorly, as the fourth branch from the arch immediately behind the point of origin of the left

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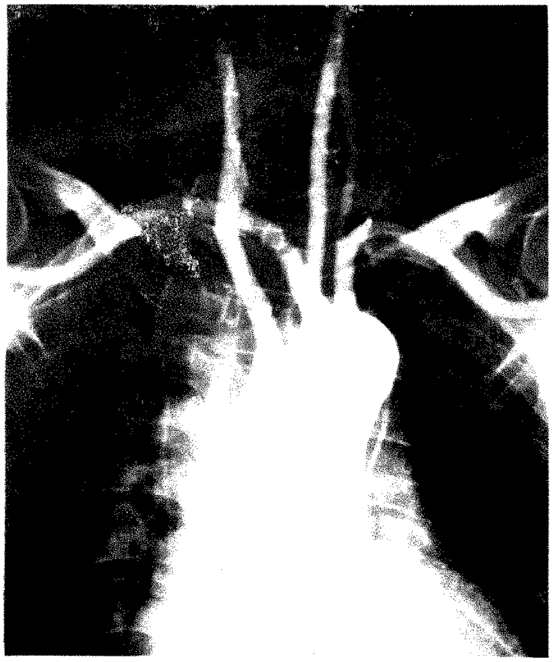


Fig. 1. Preoperative barium swallow examination showing an indentation of the oesophagus at the level of D3 suggestive of an external compression by an aberrant right subclavian artery.

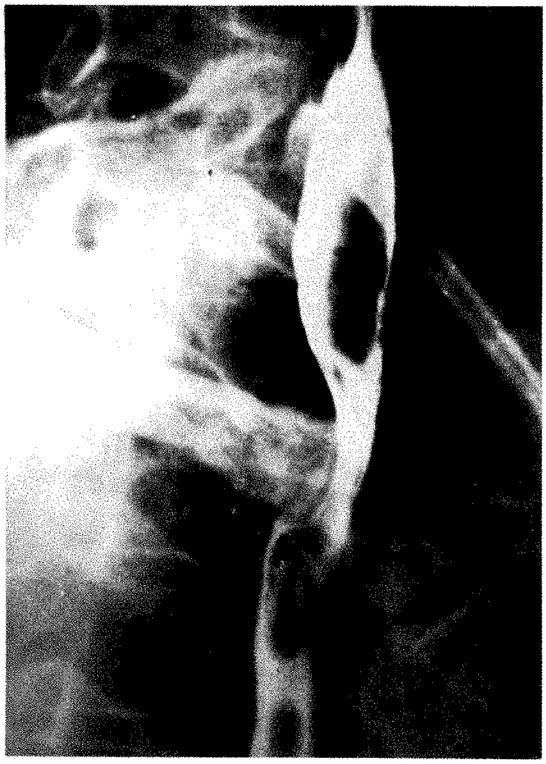


Fig. 2. Arch-aortogram demonstrating the presence of an aberrant right subclavian artery. Its origin is obscured by the overlying vessels.

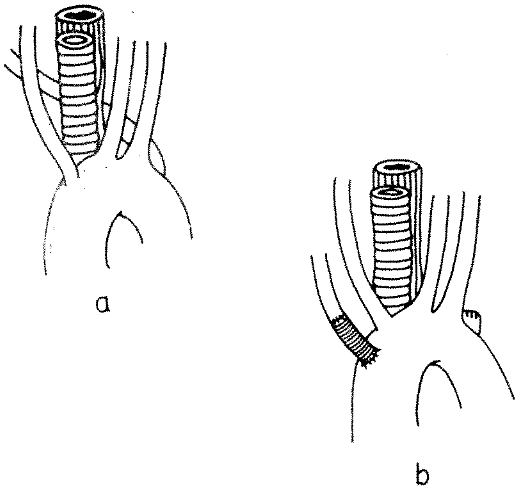


Fig. 3. Diagrams showing the preoperative (*a*) and postoperative (*b*) anatomy of the aberrant retro-oesophageal right subclavian artery.

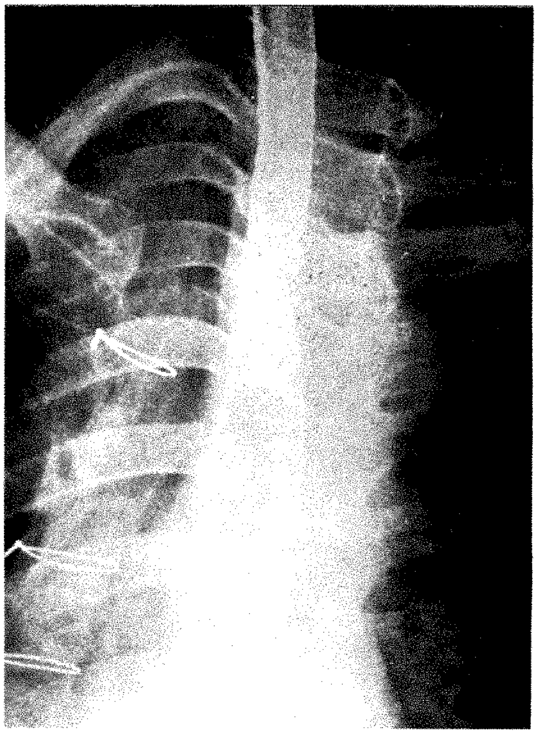


Fig. 4. Postoperative barium swallow examination confirming the removal of the oesophageal compression.

subclavian artery. It passes around the left and posterior aspects of the trachea and the oesophagus before coming to lie in the usual position to serve as the right subclavian artery (*Fig.* 3*a*). It is frequently stated that the aberrant right subclavian artery may pass in front of the oesophagus instead of behind it, or even in front of the trachea. After carefully reviewing the literature, Stewart et al. (1964) concluded that the passage of an aberrant right subclavian artery in front of the trachea or between the trachea and oesophagus must be extremely rare, if it ever occurs.

Table I: SUMMARY OF THE PUBLISHED SURGICAL APPROACHES AND TECHNIQUES FOR DIVIDING AND RECONSTITUTING THE ABERRANT RIGHT SUBCLAVIAN ARTERY IN DYSPHAGIA LUSORIA

Author	Approach	Method of division	Method of restoring pulsatile flow
Bailey et al., 1965	Right thoracotomy	Aberrant artery is transected as far into the left chest as possible	Distal right subclavian artery is reimplanted into ascending aorta posterior to SVC
Siderys, 1969	Cervical incision and left thoracotomy	Through cervical incision aberrant artery is transected at level of right carotid artery. Proximal aberrant artery is resected at its origin through a left thoracotomy	Distal right subclavian artery is anastomosed end to side to right carotid artery through cervical incision
Pifarre et al., 1971	Left thoracotomy	Aberrant artery is dissected free all the way to right side of mediastinum and transected at its origin	Dacron graft is sutured to distal right subclavian artery at retro-oesophageal position Anterior mediastinum is dissected. Subclavian artery together with Dacron graft is brought to right side of oesophagus, trachea and SVC and anastomosed end to side to aortic arch
Shumacker et al., 1971	Median sternotomy	Aberrant artery is isolated and divided at its origin. Distal artery is withdrawn from retro-oesophageal position	Distal right subclavian artery is anastomosed end to side to right carotid artery
Orvald et al., 1972	Cervical incision	Aberrant artery is identified to the right and left of oesophagus. It is divided to right of oesophagus. Proximal vessel is removed from behind oesophagus and oversewn	Distal right subclavian artery is anastomosed end to side to right carotid artery

SVC, Superior vena cava.

It appears that the mechanism of obstruction is the result of the artery lying behind the oesophagus, which is relatively well fixed between the rigid vertebral column posteriorly and the comparatively rigid trachea anteriorly. It is not clear why it produces symptoms in only a minority of those individuals with this anomaly. Klinkhamer (1966) felt that the retro-oesophageal artery is of clinical importance when the right carotid artery arises abnormally far away to the left in such a manner as to trap the somewhat flexible trachea and oesophagus and to prevent their anterior displacement at the crossing of the retro-oesophageal vessel. This is not generally accepted, however (Shumacker et al., 1971), and was not observed in our case. The mechanisms involved in the onset or aggravation of symptoms are also not understood. When symptoms occur in an adult, atherosclerotic rigidity, tortuosity and dilatation of the artery are suspected as contributing factors (Lichter, 1963). It is important to be able to recognize this anomaly as a cause of dysphagia, as corrective surgery relieves the symptoms completely.

The clinical features and radiological characteristics are well described in previous reports. The present case is of special interest in that pain, numbness of the left upper extremity and diminished radial pulse and blood pressure in the left instead of the right arm have never previously been reported in association with dysphagia lusoria. In the literature the classic description is of diminished radial pulse and blood pressure in the right rather than in the left arm (Felson et al., 1950; Shumacker et al., 1971). In the present case, since the aberrant right subclavian artery arose almost immediately behind the origin of the left subclavian artery, it might have exerted some pressure effect and impeded blood flow to the left arm. The fact that the pain and numbness disappeared completely after corrective surgery indicates that the aberrant artery was responsible for these features.

Since Gross inaugurated surgical correction of the condition in 1946, simple division through a thoracotomy has become a standard operative procedure for dysphagia lusoria. Gangrene of the upper extremity has been reported following ligation of the subclavian artery (Webb and Burford, 1952) and subclavian steal syndrome has also been described following simple division of the aberrant right subclavian artery (Pifarre et al., 1971). It would certainly seem wise to re-establish the arterial continuity in order to prevent these disabling complications.

The aberrant artery has been successfully divided and reconstituted by five different approaches and techniques (*Table I*). There is no doubt that Gross' original proposal of a left thoracotomy approach provides the best exposure of the aberrant artery at its origin. However, transposing the aberrant artery to the proximal aortic arch after division through a left thoracotomy, as suggested by Pifarre et al. (1971), is by no means a simple procedure. It involves bringing the aberrant artery from the posterior to the anterior mediastinum and two 'artery-to-graft' anastomoses deep in the mediastinum. It might be difficult to control the haemorrhage should there be bleeding from the anastomoses or slipping of the vascular clamps. Technically, it is possible to transect the aberrant artery through a right thoracotomy and reimplant the distal subclavian artery to the ascending aorta (Bailey et al., 1965). With this approach, however, a larger proximal stump than desired may be left behind. A patient with residual symptoms of dysphagia following this procedure has been reported (Pifarre et al., 1971). Besides, if bleeding occurs at the proximal stump, it will be very difficult to control it through the right thoracotomy.

Orvald et al. (1972) demonstrated that the aberrant artery could be divided and transposed through a single cervical incision. With this approach, however, the operative field is confined to the base of the neck and the thoracic inlet, and it would not be easy to control the aberrant artery at its origin should intraoperative haemorrhage occur. Siderys' combined cervical and left thoracotomy approach (Siderys,

1969) is a safer procedure, but it involves two separate incisions and positioning of the patient twice.

Since intraoperative haemorrhage and damage to the adjacent nerves and thoracic duct are the possible hazards of operating in this area, the ideal approach to the aberrant artery will be an incision that provides good exposure and full control of the aberrant artery during dissection, division and anastomosis. We find that the mediastinal approach through a median sternotomy incision, as utilized by Shumacker et al. (1971), satisfies these criteria. Early on in the operation the aberrant artery should be taped at its origin and to the right of the oesophagus. With gentle forward retraction of the oesophagus the dissection of the retro-oesophageal portion of the artery should be started from the right posterior mediastinum towards its point of origin from the aortic arch. The first portion of the aberrant artery is almost completely covered by the left carotid and left subclavian arteries. The aberrant artery should be divided to the left of the oesophagus with vascular clamps applied to the origin and just proximal to the origin of the right vertebral artery respectively.

By anastomosing the distal right subclavian artery to the right carotid artery it appears that the 'normal' anatomy is restored. There is, however, the possibility of some decrease in the blood supply to the right carotid artery, and, furthermore, in performing the end-to-side anastomosis, the partial exclusion clamp might cause transient cerebral ischaemia and damage to an atherosclerotic right carotid artery. We therefore feel that a better way of restoring pulsatile flow to the right subclavian artery is to anastomose the artery to the aortic arch with or without an interposition Dacron graft.

In our opinion, the operation of choice in dysphagia lusoria is to divide the aberrant artery at its origin through a median sternotomy and transpose the distal subclavian artery to the proximal aortic arch with or without an interposition Dacron graft.

References

ANSON B. J. (1936) The anomalous right subclavian artery: its practical significance with a report of three cases. *Surg. Gynecol. Obstet.* **62**, 708–711.

BAILEY C. P., HIROSE T. and ALBA J. (1965) Re-establishing the continuity of the anomalous right subclavian artery after operation for dysphagia lusoria. *Angiology* **16**, 509–513.

BAYFORD D. (1789) *Memoirs of the Medical Society of London*, vol. 2. London, Medical Society of London, p. 271 (2nd ed., p. 275).

FELSON B., COHEN S., COURTER S. R. et al. (1950) Anomalous right subclavian artery. *Radiology* **54**, 340–349.

LINDBLOOM A. A. (1922) The anomalous right subclavian artery and its possible clinical significance. *Surg. Gynecol. Obstet.* **34**, 378–384.

GROSS R. E. (1946) The surgical significance of aortic arch anomalies. *Ann. Surg.* **124**, 532–534.

HOLZAPFEL G. (1899) Ungewöhnlicher Ursprung und Verlauf der Arteria subclavia dextra. *Anat. Hefte* **12**, 369–523.

HUNAULD P. (1935) Examen de quelques parties d'un singe. *Hist. Acad. R. Sc.* **2**, 516–523.

KLINKHAMER A. C. (1966) Aberrant right subclavian artery. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **97**, 438–446.

KOMMERELL B. (1936) Verlagerung des Ösophagus durch eine abnorm verlaufende Arteria subclavia dextra (Arteria lusoria). *Fortschr. Geb. Roentgenstr.* **54**, 590–595.

LICHTER I. (1963) The treatment of dysphagia lusoria in the adult. *Br. J. Surg.* **50**, 793–796.

MORRIS R. (1960) Dysphagia lusoria presenting as a superior mediastinal syndrome. *Br. Med. J.* **2**, 1558–1561.

ORVALD T. O., SCHEERER R. and JUDE J. R. (1972) A single cervical approach to aberrant right subclavian artery. *Surgery* **71**, 227–230.

PIFARRE R., DIETER R. A. jun. and NIEDBALLA R. G. (1971) Definitive surgical treatment of the aberrant retro-oesophageal right subclavian artery in the adult. *J. Thorac. Cardiovasc. Surg.* **61**, 154–159.

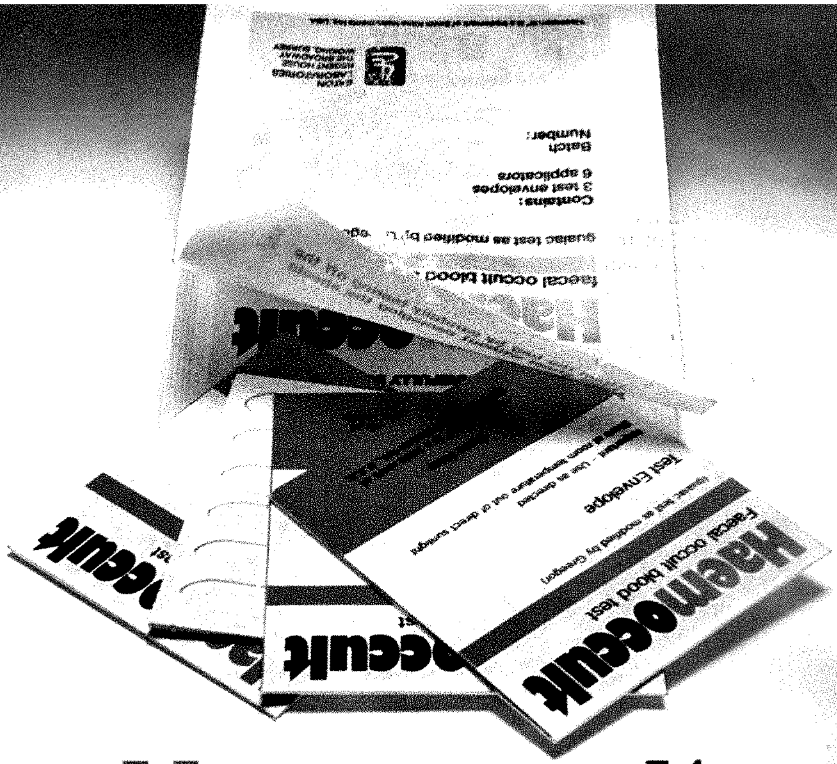
SIDERYS H. (1969) A new operation for symptomatic aberrant right subclavian artery in the adult (dysphagia lusoria). *J. Thorac. Cardiovasc. Surg.* **57**, 269–272.

SHUMACKER H. B. jun., ISCH J. H. and FINNERAN J. C. (1971) Unusual case of dysphagia due to anomalous right subclavian artery. *J. Thorac. Cardiovasc. Surg.* **61**, 304–308.

STEWART J. R., KINCAID O. W. and EDWARDS J. E. (1964) *An Atlas of Vascular Rings and Related Malformations of the Aortic Arch System.* Springfield, Ill., Thomas, p. 53.

WEBB W. R. and BURFORD T. H. (1952) Gangrene of the arm following use of the subclavian artery in a pulmono-systemic (Blalock) anastomosis. *J. Thorac. Cardiovasc. Surg.* **23**, 199–204.

Paper accepted 22 June 1978.



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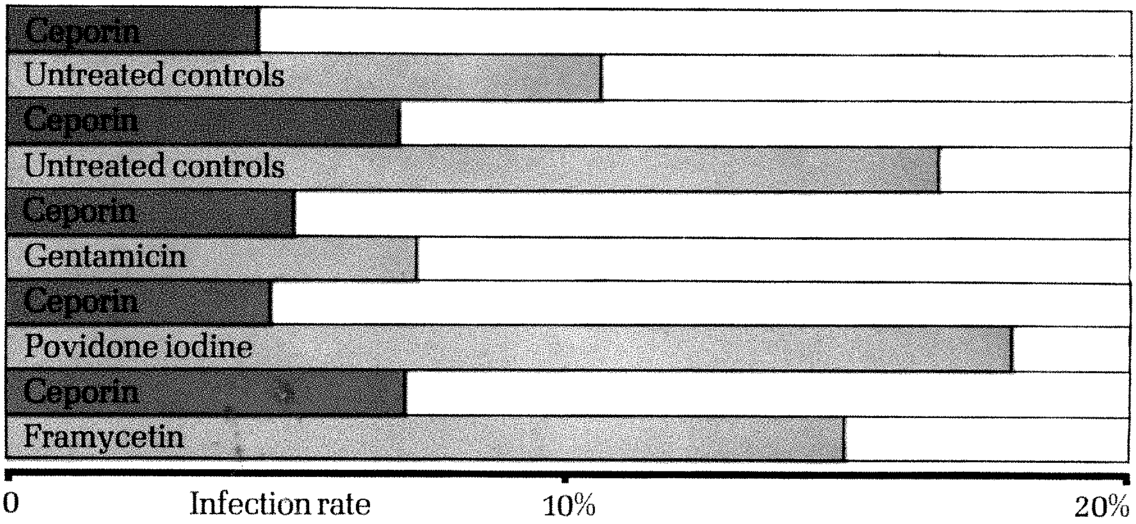

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Gastric carcinoma and previous peptic ulceration

D. J. ELLIS, R. D. KINGSTON, V. S. BROOKES AND J. A. H. WATERHOUSE*

SUMMARY

The incidence of patients with gastric carcinoma having had a previously diagnosed or suspected peptic ulcer was noted in two studies. These studies were the West Midlands Gastric Chemotherapy Trial (1974–6) and a retrospective study of patients presenting to the United Birmingham Hospitals with gastric carcinoma during the years 1958–62 and 1968–72.

The incidence of patients found to have had a previous operation for duodenal ulcer or to have post-mortem evidence of one was 6·5 per cent and 5·7 per cent respectively. A radiologically proved duodenal ulcer had been identified in 5·5 per cent and 2·1 per cent respectively and the incidence of previous symptoms suggestive of a duodenal ulcer was 4·0 per cent and 5·2 per cent. These figures indicate the total incidence could be 12·97–16·0 per cent, which is much higher than previously reported.

The mean time interval between operation for duodenal ulcer and the development of gastric carcinoma was much longer in patients having had a partial gastrectomy than in patients having had a vagotomy and drainage procedure.

The incidence of previous benign gastric ulcers was 2·5 per cent and 0·9 per cent. Fifty-three per cent of patients having had a previous operation for duodenal ulceration were found to have an unresectable carcinoma, compared with the overall unresectable rate of 35 per cent.

THE relationship of chronic benign gastroduodenal conditions to gastric carcinoma has been studied by several authors (De Jode, 1961; Burns and Taubman, 1967; Stalsberg and Taksdal, 1971; Nicholls, 1974). Most of the information has come from retrospective surgical or post-mortem studies, with the result that those cases not treated surgically or not coming to post-mortem have been excluded.

In the course of a recent trial of cytotoxic chemotherapy for patients with unresectable gastric carcinoma in the West Midlands (Kingston et al., 1978), we noted an unusual number of patients with previously diagnosed or suspected peptic ulcer and in particular with duodenal ulcer. These cases were analysed in detail and subsequently a retrospective survey of a larger group of patients with gastric carcinoma was undertaken.

Patients and methods

The West Midlands Chemotherapy Trial (WMCT) involved 200 patients with unresectable gastric carcinoma. The retrospective survey was based on all patients with gastric carcinoma admitted to the United Birmingham Hospitals (UBH) over two separate periods, each of 5 years, a decade apart (1958–62 and 1968–72 inclusive). The separate periods were selected because vagotomy and pyloroplasty had superseded partial gastrectomy as the operation of choice for duodenal ulcer in Birmingham in the early 1960s, and the two groups might therefore reflect differences in the relationship of a particular operation to subsequent carcinoma of the stomach.

In the 10 years studied the numbers of cases notified to the Birmingham Cancer Registry from the UBH were as follows: in 1958–62 410 cases were notified, of which full records were available in 386 (94 per cent); during 1968–72, 452 cases were notified, of which 440 ([illegible] per cent) had full records available; a total of 826 patients were thus studied in the UBH group.

In both the WMCT and the UBH groups the medical histories of the cases were reviewed and any patients with previous history of duodenal or gastric ulceration were divided into the following categories:

1. Previous surgery: (*a*) partial gastrectomy; (*b*) gastro-enterostomy; (*c*) vagotomy and drainage procedure; (*d*) simple suture of perforation.
2. Chronic peptic ulcer found at operation for gastric carcinoma or at post-mortem.
3. Previous barium meal evidence of a peptic ulcer.
4. Previous dyspeptic symptoms requiring medical treatment (at least 5 years before the diagnosis of gastric carcinoma).

All information was obtained from the hospital records and/or Cancer Registry records.

Results

The WMCT showed 13 patients to have had previous surgery for duodenal ulcer, 11 had had radiological evidence of duodenal ulcer and 8 had previous dyspeptic symptoms.

In the period 1958–62 there were 20 patients who had had a previous operation for duodenal ulcer. In addition, 2 patients had definite evidence of duodenal ulceration (i.e. chronic ulcer at operation for gastric carcinoma or at post-mortem). Seven patients had had previous radiological evidence of duodenal ulcer and 20 patients had previous dyspeptic symptoms requiring medical treatment.

In the period 1968–72 there were 22 patients who had had a previous operation for duodenal ulcer, and 3 patients had definite evidence of duodenal ulcer (i.e. chronic ulcer at operation for gastric carcinoma or at post-mortem). Ten patients had had radiological evidence of duodenal ulcer and 23 patients had previous dyspeptic symptoms.

The combined results are shown in *Table I*.

There does seem to be a marked difference in the time interval between patients developing cancer of the stomach after partial gastrectomy for duodenal ulcer and those who developed carcinoma after previous vagotomy and pyloroplasty for duodenal ulcer. *Table I* shows that in the UBH group the mean time interval between partial gastrectomy for duodenal ulcer and the development of gastric carcinoma was 24·2 years and in the WMCT it was 18·7 years. In patients who had previously undergone vagotomy and pyloroplasty for duodenal ulcer the mean time interval between that operation and the development of gastric carcinoma was 6 years in the UBH group and 5·4 years in the WMCT group.

In the two 5-year periods studied in the UBH group there was in fact no real difference between the numbers of patients undergoing partial gastrectomy for duodenal ulcer and those undergoing vagotomy and pyloroplasty.

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Table I: THE EVIDENCE FOR PREVIOUS PEPTIC ULCERATION IN 1026 PATIENTS WITH GASTRIC CARCINOMA

	WMCT ($n = 200$)			UBH ($n = 826$)			
		% of total	Time interval between DU and Ca. (mean yr)	No.	% of total	Time interval between DU and Ca. (mean yr)	Total for both series
Previous operation for DU							
Partial gastrectomy		3·0	18·7	15	1·82	24·2	21
Gastroenterostomy		0·5	39·0	13	1·57	31·4	14
Vagotomy and pyloroplasty	5	2·5	5·4	6	0·73	6·0	11
Simple suturing of perforated DU	1	0·5	4·0	8	0·97	24·6	9
Total	13	6·5	—	42	5·09	—	55 (5·36%)
Chronic DU found at operation for carcinoma or at post-mortem	—	—	—	5	0·61	—	5
Radiological evidence for DU	11	5·5	20·5	17	2·06	11·8	28
Previous history of DU	8	4·0	17·6	43	5·21	17·6	51
Total possible DU	19	9·5	—	65	7·88	—	84 (8·19%)
Benign GU	5	2·5	15·4	7	0·85	13·4	12 (1·17%)

DU, Duodenal ulcer; GU, gastric ulcer.

Table II: STUDIES OF THE ASSOCIATION OF CHRONIC BENIGN GASTRODUODENAL CONDITIONS AND GASTRIC CARCINOMA

Centre	Reference	No. cases	Duodenal ulcers	Gastric ulcers
St James', London	Nicholls, 1974	1473	3 (0·20%)	14 (0·95%)
London Hospital, London	De Jode, 1961	1000	12 (1·20%)	6 (0·60%)
Lausanne, Switzerland	Saegesser and James, 1972	725	15 (2·06%)	3 (0·41%)
Oslo, Sweden	Stalsberg and Taksdal, 1971	500	3 (0·60%)	3 (0·60%)

Of the 826 patients of the UBH group, only 7, and of the WMCT group, only 5, patients had evidence of gastric ulcer, compared with the total of 60 cases of proved duodenal ulcer and 79 probable duodenal ulcers.

Discussion

Of the total of 1026 patients studied in the two groups, 55 (5·4 per cent) had previously had an operation for duodenal ulcer—a much higher incidence than has previously been reported (*Table II*). A further 33 patients (3·2 per cent of the total) had a duodenal ulcer confirmed at the time of operation for the carcinoma, at post-mortem or by previous radiological studies. The confirmed incidence of previous duodenal ulcer was therefore 8·6 per cent. In addition, 51 patients (5·0 per cent) had had a long history of dyspepsia typical of duodenal ulcer at least 5 years before the onset of symptoms referrable to the carcinoma. Since there was no absolute confirmation of the ulcer diagnosis in these cases, the validity of the last category may be open to question, but it is not unreasonable to conclude that the overall incidence is greater than that in the positively proved cases (8·6 per cent) above.

These figures give no indication of the number of people suffering from a duodenal ulcer who eventually develop gastric carcinoma. Nicholls (1974) attempted to define the number of patients who, in the long term, develop a gastric carcinoma following a partial gastrectomy for a duodenal ulcer. The figure reached was 1 in 865 patients. In his study follow-up was known not to be complete, and it relates only to partial gastrectomy, with no patients included who had not undergone surgery. In view of the difficulty in establishing a reliable figure for the incidence of duodenal ulcer in the general population, a long term general practice survey, including all patients with a proved duodenal ulcer, would be required to find the true total incidence of subsequent gastric carcinoma.

It is interesting to speculate as to the possible mechanism of how gastric carcinoma arises in patients who have or have had a duodenal ulcer. A relationship between chronic gastritis and gastric carcinoma has been shown to exist by several workers (Magnus, 1937; Strickland et al., 1970; Imai et al., 1971; Du Plessis, 1974) and carcinoma develops more commonly when cellular hyperplasia (Chusid et al., 1964) or metaplasia (Morson, 1955a, b) is present. Mucosal changes may be initiated by gastric stasis (Dragstedt and Woodward, 1963; Dragstedt, 1965), or bile reflux producing chronic gastritis (Lawson, 1964; Capper, 1967; Capper et al., 1967).

Gouch and Craven (1975) believe that there is sufficient clinical, pathological and experimental evidence to support the view that a gastrojejunal anastomosis is a premalignant condition. Lawson (1965) showed that in about 100 per cent of cases of a gastrojejunal anastomosis there was an associated chronic gastritis, but that gastritis was much less common after pyloroplasty or a Billroth I anastomosis.

It was noted in our studies that the mean time interval between surgery for a duodenal ulcer and the development of gastric carcinoma was much longer following a partial gastrectomy. The shortest interval for partial gastrectomy was 4 years and the longest 43 years, with a mean of 24 years, while the range for vagotomy and drainage was 2 to 18 years with a mean of 6 years. The significance of this finding in the small number of patients studied is limited, but if this was a true trend then it may be another indication for performing a partial gastrectomy for duodenal ulceration. It is possible that gastric atrophy leading to mucosal changes occurs more rapidly following vagotomy and drainage than partial gastrectomy. Further, it is generally recognized that 45 per cent of all gastric carcinomas arise at the pylorus and antrum; hence, removing this area and two-thirds of the stomach must be one important means of preventing a future carcinoma developing.

A significantly increased incidence of gastric carcinoma developing in the gastric stump following partial gastrectomy for gastric ulcer has been demonstrated (Nicholls, 1974). One in every 76 patients developed a carcinoma a minimum of 3 years after surgery. This is strikingly higher than the normal population incidence and strongly indicates a mucosal rather than an extrinsic factor such as diet as the cause.

Evidence would indicate that chronic gastritis is the premalignant condition common to the whole range of duodenal ulcer patients, i.e. non-operative and postoperative patients.

Our total incidence of previously diagnosed benign gastric ulcers was 1·17 per cent. This is higher than other reports (Fischer et al., 1947; De Jode, 1961; Stalsberg and Taksdal, 1971; Saegesser and James, 1972; Nicholls, 1974), which have only taken account of operations for gastric ulcer and not included radiologically diagnosed, medically treated ulcers.

This incidence relates very closely to the previously reported association between gastric ulcer and gastric carcinoma in the West Midlands (Brookes et al., 1965). In that series the incidence of proved gastric ulcer was only 1·5 per cent. This compares dramatically with the 8·6 per cent incidence of previous duodenal ulcer.

As described in other reports (Debray et al., 1958; Yanishevsky and Klimenkov, 1968; Nicholls, 1974), we noted the high number of patients with unresectable carcinoma in the group who had had previous surgery for a duodenal ulcer, 53 per cent of this group being unresectable compared with 35 per cent overall. This high unresectability rate is probably due to failure on the part of the clinician to suspect carcinoma in these patients. Other reports (Pygott and Shah, 1968; Graves and Herrington, 1971) have stressed the fact that any patient presenting with further dyspeptic symptoms more than 5 years after surgery for peptic ulcer should be suspected of having developed a gastric stump carcinoma and not a stomal ulcer, which tends to present within 5 years.

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References

BROOKES V. S., WATERHOUSE J. A. H. and POWELL J. (1965) Cancer of the stomach: a 10-year survey of results and of factors affecting prognosis. *Br. Med. J.* **1**, 1577–1583.

BURNS G. P. and T[illegible] J. (1967) The association of gastric carcinoma with duodenal ulcer. *Br. J. Surg.* **54**, 174–176.

CAPPER W. M. (19[illegible]7) Factors in the pathogenesis of gastric ulcer. *Ann. R. Coll. Surg. Engl.* **40**, 21–35.

CAPPER W. M., BUTLER T. J., KILBY J. O. et al. (1967) Gallstones, gastric secretions and flatulent dyspepsia. *Lancet* **1**, 413–415.

CHUSID E. L., H[illegible] and COLCHER H. (1964) Spectrum of hypertro[illegible] *Arch. Intern Med.* **114**, 621–628.

DEBRAY V. C[illegible] ROCHES P. (1958) Stump carcinoma after gast[illegible] for ulcer *Schweiz. Med. Wochenschr.* **88**, 631–634.

DRAGSTEDT L. R. (1965) Gastrin and peptic ulcer. *Arch. Surg.* **91**, 1005–1010.

DRAGSTEDT L. R. and WOODWARD E. R. (1963) Co-existent duodenal and gastric ulcers treated by vagotomy and pyloroplasty. *JAMA* **184**, 1014–1017.

FISCHER A., THERON CLAGETT O. and MCDONALD J. R. (1947) Co-existent duodenal ulcer and gastric malignancy. *Surgery* **21**, 168–174.

GOUCH D. C. and CRAVEN J. L. (1975) Is a gastro-enterostomy a pre-malignant condition? *Gut* **16**, 843.

GRAVES H. A. and HERRINGTON J. L. (1971) Gastric carcinoma developing after surgery for peptic ulcer. *Am. Surg.* **37**, 73–76.

IMAI T., KUBO T. and WATANABE H. (1971) Chronic gastritis in Japanese with reference to high incidence of gastric carcinoma. *J. Natl Cancer Inst.* **47**, 179–195.

DE JODE L. R. (1961) Gastric carcinoma following gastro-enterostomy and partial gastrectomy. *Br. J. Surg.* **48**, 512–514.

KINGSTON R. D., ELLIS D. J., POWELL J. et al. (1978) The West Midlands Gastric Carcinoma Chemotherapy Trial: planning and results. *Clin. Oncol.* **4**, 55–69.

LAWSON H. H. (1964) Effect of duodenal contents on the gastric mucosa under experimental conditions. *Lancet* **1**, 469–472.

LAWSON H. H. (1965) Effect of duodenal contents on the gastric mucosa under experimental conditions. *S. Afr. J. Surg.* **3**, 79–92.

MAGNUS H. A. (1937) Observations on the presence of intestinal epithelium in the gastric mucosa. *J. Pathol. Bacteriol.* **44**, 389–398.

MORSON B. C. (1955a). Intestinal metaplasia of the gastric mucosa. *Br. J. Cancer* **9**, 365–376.

MORSON B. C. (1955b) Carcinoma arising from areas of intestinal metaplasia in the gastric mucosa. *Br. J. Cancer* **9**, 377–385.

NICHOLLS J. C. (1974) Carcinoma of the stomach following partial gastrectomy for benign gastro-duodenal lesions. *Br. J. Surg.* **61**, 244–249.

DU PLESSIS D. J. (1974) The distribution of gastritis in carcinoma of the stomach. *Br. J. Surg.* **61**, 521–523.

PYGOTT F. and SHAH V. L. (1968) Gastric cancer associated with gastro-enterostomy and partial gastrectomy. *Gut* **9**, 117–124.

SAEGESSER F. and JAMES D. (1972) Cancer of the gastric stump after partial gastrectomy (Billroth II principle) for ulcer. *Cancer* **29**, 1150–1159.

STALSBERG H. and TAKSDAL S. (1971) Stomach cancer following gastric surgery for benign conditions. *Lancet* **2**, 1175–1177.

STRICKLAND R. G., UNGAR B. and MACKAY I. R. (1970) Natural history of chronic atrophic gastritis. *Aust. Ann. Med.* **19**, 419.

YANISHEVSKY V. J. and KLIMENKOV A. A. (1968) Repeated operations for cancer in the residual stomach after gastric resection. *Acta Med Pol.* **9**, 421–424.

Paper accepted 26 July 1978.

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A reappraisal of the value of carcinoembryonic antigen in the management of patients with various neoplasms

M. J. COOPER, C. R. MACKIE, D. B. SKINNER AND A. R. MOOSSA*

SUMMARY

Eight hundred and eight patients with histologically proved malignant disease had carcinoembryonic antigen (CEA) estimations performed at the time of tissue diagnosis. An elevated level was found in 384 of 518 patients with gastrointestinal neoplasms (74 per cent) and in 162 of 290 patients with other neoplasms (56 per cent). No correlation was found between CEA elevations and tumour differentiation. There was a good correlation between tumour staging and CEA levels for patients with colorectal cancer; the more advanced the tumour, the higher the CEA.

Several illustrative cases are presented and the role of CEA assay in the diagnosis and management of neoplasia is discussed. CEA assay is a poor screening test for neoplastic disease, but serial CEA monitoring is valuable in the detection of residual or recurrent cancer.

CARCINOEMBRYONIC antigen (CEA) was first described by Gold and Freedman in 1965 and was hailed as a specific tumour marker for colonic cancer (Thompson et al., 1969; Nugent and Hansen, 1971). Further studies with this antigen have shown that levels are elevated in a large proportion of patients with a variety of malignant and benign diseases (Zamcheck et al., 1972; Martin et al., 1976). Its value in the diagnosis and management of neoplastic disease needs to be redefined. We have correlated the results of all CEA estimations over the past 5 years in patients with histologically proved malignant disease and have studied several cases serially to demonstrate the value of CEA estimation in prognosis and management.

Patients and methods

Between March 1972 and January 1978, CEA estimations were performed on sera from 808 patients with histologically proved malignant disease at the University of Chicago. All assays were performed by the Hansen Z-gel method (Hansen et al., 1971) (Hoffman–LaRoche Inc.), a normal value being less than 2·5 μg/l; all determinations were first performed by the indirect method and those sera with a value greater than 20 μg/l were re-evaluated by the direct method. The initial CEA levels were recorded within 6 weeks of a tissue diagnosis being obtained, and all values were correlated with the surgical pathology reports. In those patients with cancers of the gastrointestinal tract note was taken of the histological differentiation; and for colonic cancers the staging was recorded by the revised Dukes' method of Astler and Coller (1954).

Results

A CEA level was obtained for 290 patients with a variety of non-gastrointestinal neoplasms; 56 per cent of this group had a CEA greater than 2·5 μg/l at the time of tissue diagnosis, and 60 per cent produced an elevated CEA at some time (*Table I*). There was a total of 526 gastrointestinal neoplasms; an elevated CEA was produced by 76 per cent of the adenocarcinomas, 60 per cent of the squamous carcinomas and 75 per cent of the APUD tumors (*Table II*). The CEA level in patients with various gastrointestinal neoplasms was compared with cellular differentiation (*Fig.* 1); no correlation could be found. In patients with colorectal cancer, the most advanced tumours as determined by the modified Dukes' classification gave rise to the highest percentage of elevated CEA levels (*Fig.* 2).

Table I: RESULTS OF CEA ASSAYS ON PATIENTS WITH NON-GASTROINTESTINAL NEOPLASMS

Primary neoplasm	No. of patients	CEA > 2·5 μg/l: At time of tissue diagnosis (%)	CEA > 2·5 μg/l: At any time (%)
Lung	54	66·7	72·2
Breast	54	68·5	72·2
Kidney	9	66·7	66·7
Hodgkin's disease	18	22·2	27·8
Prostate	21	66·7	71·4
Testis	2	50	50
Gynaecological (misc.)	18	66·7	66·7
Thyroid	4	50	50
Bladder	10	60	60
Lymphoma (non-Hodgkin)	32	15·6	18·8
Sarcoma (misc.)	5	0	20
Skin (misc.)	10	30	40
Total	290	55·9	60·3

Table II: RESULTS OF CEA ASSAYS ON PATIENTS WITH GASTROINTESTINAL NEOPLASMS

Primary neoplasm	No. of patients	CEA > 2·5 μg/l: At time of tissue diagnosis (%)	CEA > 2·5 μg/l: At any time (%)
Oropharynx (squamous)	39	58·8	58·8
Oesophagus (squamous)	18	61·6	66·7
Stomach (adeno)	69	59·4	78·3
Cholangiocarcinoma	11	72·7	100
Hepatoma	12	75	75
Pancreas (adeno)	77	80·5	89·6
APUD tumours	8	75	75
Small bowel (adeno)	6	83·3	83·3
Colon (adeno)	283	78·8	86·2
Anus (squamous)	3	66·7	100
Total			
Adenocarcinoma	458	76	85·6
Squamous cancer	60	60	63·3

Fig. 3 illustrates results in 4 representative patients with colorectal cancer.

Case 1: D. B., a 78-year-old female, presented in April 1978 with a 3-year history of change of bowel habit. A CEA level was >1200 μg/l and barium enema revealed a caecal cancer. She underwent a right radical hemicolectomy for a well-differentiated C2 cancer, and 1 month later her CEA had fallen

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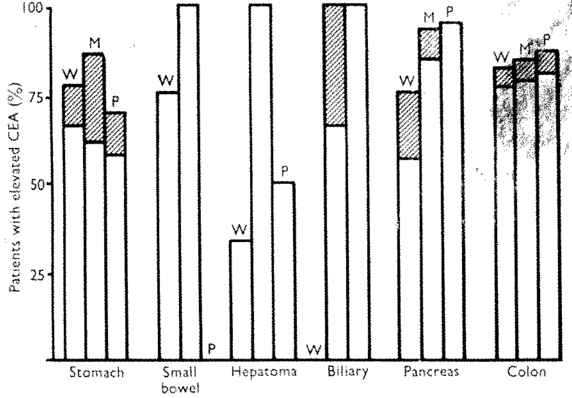


Fig. 1. Patients with gastrointestinal neoplasms divided by cellular differentiation (W, well, M, moderately and P, poorly differentiated) showing the percentage with an elevated CEA at the time of tissue diagnosis (white bars) and the total percentage that develop an elevation at any time (hatched bars).

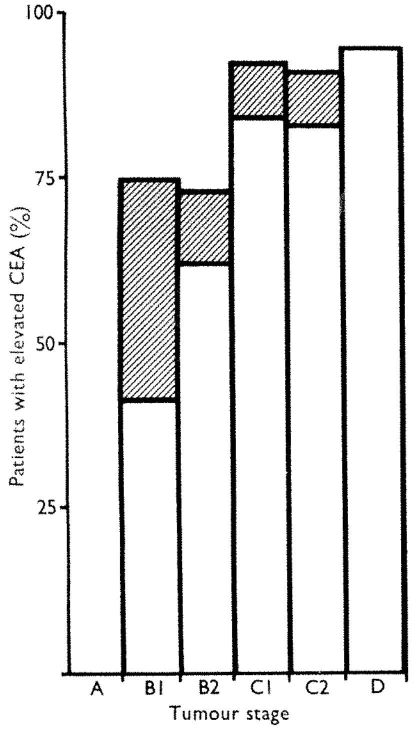


Fig. 2. Patients with colorectal cancer divided by stage showing the percentage with an elevated CEA at the time of tissue diagnosis (white bars) and the total percentage that develop an elevation at any time (hatched bars).

to 4 µg/l. The CEA then rose to 6 µg/l at 3 months, and 185 µg/l at 9 months; liver scan and chest X-ray at that time revealed multiple metastases.

Case 2: H. D., a 70-year-old female, presented in December 1975 with a change of bowel habit. Investigation revealed a colonic mass and a CEA of 9·6 µg/l. A colectomy was performed for a moderately differentiated C2 cancer of the descending colon. In June 1976 a repeat CEA was still elevated at 7·6 µg/l and further investigation revealed a small rectal tumour (<1 cm in diameter). Following an abdomino-perineal resection CEA levels fell to normal and the patient remains symptom-free with normal CEA levels 18 months later.

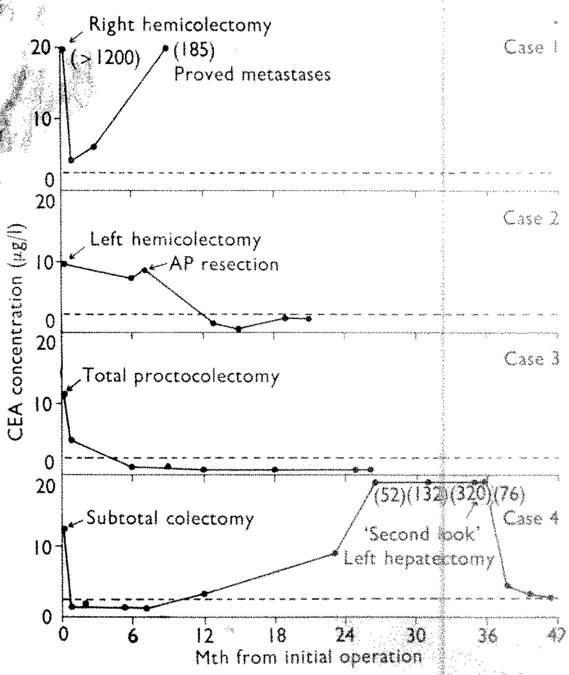


Fig. 3. Results of serial CEA estimations performed on 4 patients with colorectal cancer.

Case 3: M. H., a 41-year-old female with known ulcerative colitis, was seen in January 1975 when a routine check-up disclosed two colonic strictures. Her CEA at this time was 11·2 µg/l. A total proctocolectomy was performed for a moderately differentiated B2 cancer of the splenic flexure, and her CEA levels fell to normal. She is clinically free of tumour with normal CEA levels 2 years later.

Case 4: H. B., a 69-year-old male, presented in November 1973 with a change in bowel habit. Investigation revealed two colonic cancers and a CEA of 12·4 µg/l. Subtotal colectomy was performed for two moderately differentiated C2 cancers and the CEA fell to 1·2 µg/l. Serial CEA levels began to rise 12 months postoperatively and reached 52 µg/l at 28 months; investigations at this time showed no evidence for recurrent or metastatic disease. The CEA remained elevated and, on this evidence alone, a 'second look' laparotomy was performed at 36 months. A solitary metastasis in the left lobe of the liver was removed; CEA concentration was 2·8 µg/l 6 months later.

Discussion

Several antigens have now been described that are present in significant amounts only in neoplastic and fetal tissues (Gold and Freedman, 1965; Abelev, 1974; Gelder et al., 1978). The development of radioimmunoassays allows reliable measurement of the plasma concentrations of these antigens, and several have now been evaluated as tumour markers. The description by Gold (Gold and Freedman, 1965) of CEA and initial reports of its specificity for entodermal cancers (Thompson et al., 1969; Nugent and Hansen, 1971) provoked widespread interest, and it is now the most thoroughly evaluated of the oncofetal antigens. Several assay techniques have been described for CEA: we have employed the Hansen Z-gel method (Hansen et al., 1971), which has been manufactured

Table III: NUMBER OF PATIENT[illegible] AN ELEVATED CEA

	No. of patients in group	No. of patients with a CEA greater than 2·5 µg/l	10·0 µg/l
Pancreatic cancer patients	52	[illegible]	20 (39%)
Other cancer patients	51	[illegible]	16 (31%)
Benign disease patients	[illegible]	31 (46%)	4 (6%)

Table IV: THE DIAGNOSTIC ABILITY OF AN ELEVATED CEA FOR MALIGNANT DISEASE TAKING TWO UPPER LIMITS OF NORMALITY

	CEA > 2·5 µg/l (%)	CEA > 10·0 µg/l (%)
Prevalence	60·6	60·6
Sensitivity	73·8	35·0
Specificity	53·7	94·0
Accuracy	65·9	58·0
Predictive value of a positive test	71·0 (3·1%)*	90·0 (10·6%)*
Predictive value of a negative test	57·1 (99·0%)*	48·5 (98·6%)*

The predictive value of a positive test is (true positive tests/all positive tests), and the predictive value of a negative test is (true negative tests/all negative tests).
* These predictive values may be recalculated and projected to a theoretical population with a 2 per cent prevalence of malignant disease, as shown in parentheses (Vecchio, 1966).

into kits by Hoffman–LaRoche. This assay is relatively simple, although it involves several steps and is time-consuming.

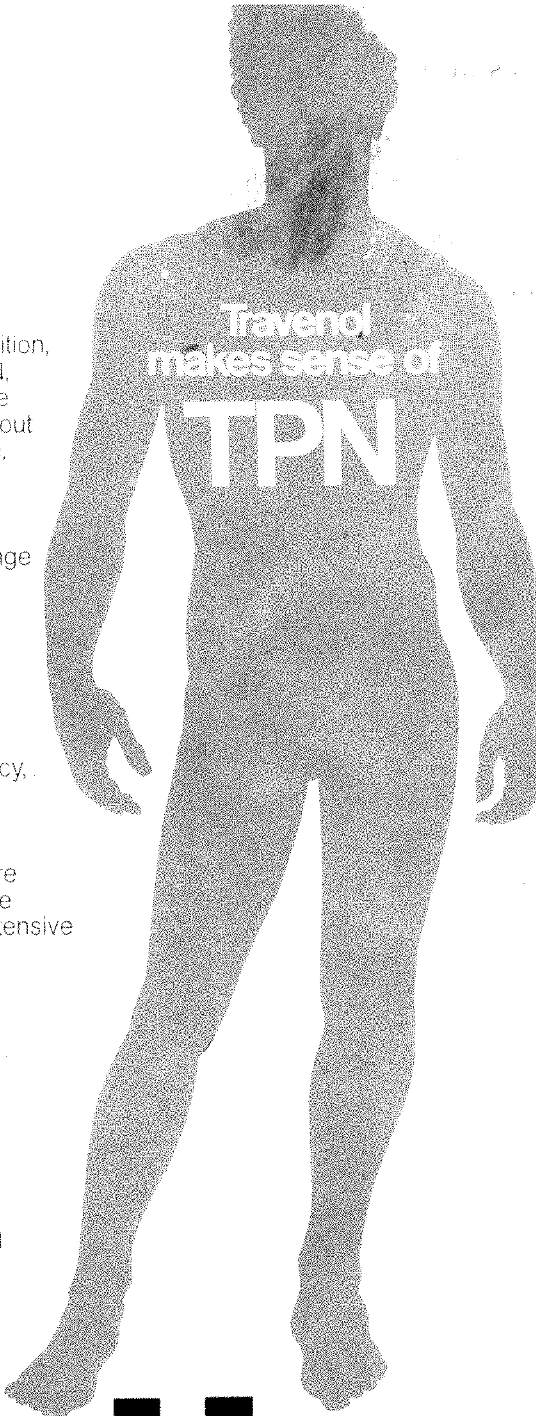
Experience with this assay in over 10 000 patients from Europe and America has shown that 97 per cent of normal people have a value less than 2·5 µg/l; the remaining 3 per cent tending to be heavy smokers (Roche Diagnostics, 1976). Initial evaluation of CEA in colonic cancer patients revealed an elevated level in 96 per cent (Thompson et al., 1969), but this was a selected group with advanced disease and a more realistic figure is around 80 per cent (Zamcheck, 1975; Martin et al., 1976). Further evaluation of CEA found values greater than 2·5 µg/l in patients with a variety of gastrointestinal tumours, particularly of the pancreas (Khoo and Mackay, 1973; Dilwari et al., 1975), where 90 per cent positive results have been frequently reported, and also in other malignant disorders, though the percentage of positive results is not as high (Stewart et al., 1974; DiSaia et al., 1977). Our figures (*Tables I, II*) are in agreement with published series.

CEA assay cannot provide a reliable screening test for malignant neoplasms as levels are frequently elevated in patients with benign disease. Elevated levels have been found in association with pancreatitis (Dilwari et al., 1975), cholecystitis (Martin et al., 1976), inflammatory bowel disease (Martin et al., 1976), liver disease (Bullen et al., 1977) and rectal polyps (Doos et al., 1975; Martin et al., 1977). While this reduces the value of CEA assay as a screening test for malignant disease, an elevation can be used to monitor these diseases. Bullen et al. (1977) found an elevated CEA in up to 70 per cent of patients with liver disease and found the CEA level to be useful in distinguishing acute from chronic liver damage. Martin et al. (1977) reported an elevated CEA in 40 per cent of patients with rectal polyps and noted that he level fell to normal after polypectomy. It has been suggested that the value of CEA as a screening test for malignant disease could be improved by taking a level of 10 µg/l as the upper limit of normal (Concannon et al., 1973, 1974). CEA levels were assayed as part of a prospective diagnostic protocol for pancreatic cancer at this institution and the results have been reported elsewhere (Wood and Moossa, 1977). To illustrate the effect of increasing the upper limit of normal from 2·5 to 10 µg/l we have evaluated the test in a group of 170 patients (*Tables III, IV*).

From *Table III* it can be seen that while 83 per cent of pancreatic cancer patients had a CEA of over 2·5 µg/l, so did 46 per cent of patients with benign disease. The effect of increasing the upper limit of normal to 10 µg/l is to reduce the positive results in benign disease to 6 per cent, at the expense of a large drop in the positive results for pancreatic cancer (39 per cent). The predictive value of a positive test must remain significantly greater than the prevalence of the disease sought (Vecchio, 1966); an effective screening test requires a high predictive value for a positive test to minimize the number of patients without malignant disease being subjected to further, and sometimes extensive, investigation. These values are shown in *Table IV* for a highly selected group of patients. When they are projected to a theoretical population with a 2 per cent prevalence of malignant disease (figures in parentheses in *Table IV*), a better estimation of the value of CEA as a screening test can be obtained. It is evident that the preferred normal level is 10 µg/l as a minimal loss in the predictive value of a negative test results in a threefold increase in the predictive value of a positive test. Even at this level, however, only 1 in 10 of the patients with a positive CEA will have malignant disease. CEA assay is thus a poor screening test for malignant disease.

A good correlation has been found between positive CEA tests and tumour staging (Zamcheck et al., 1972; Martin et al., 1976). Furthermore, the larger the tumour mass, the more CEA is produced, the highest levels being found in patients with metastatic disease, as shown in *Fig.* 2. Some authors (Martin et al., 1976) have shown that more CEA is produced by the better differentiated tumours, but we are unable to confirm this finding (*Fig.* 1); our results show no correlation between cellular differentiation and CEA levels. The effect of differentiation is difficult to estimate on its own, as the well-differentiated tumours are sometimes small and therefore less likely to produce large amounts of CEA. *Tables I* and *II* show that a small percentage of patients with an initially normal CEA develop elevations during the course of their disease. The clinical significance of this observation has not been fully evaluated and requires further investigation.

Attention has turned to the ability of serial CEA assay to detect recurrent or residual tumour at an early stage (Dhar et al., 1972; Sugarbaker et al., 1976; Martin et al., 1977). The success of Ellis and others with 'second look' procedures has prompted a more aggressive approach to the management of recurrent cancer; the success of these operations relies on early detection of recurrent tumour. An elevated CEA should fall to normal within 1 month of curative resection of a cancer (Zamcheck, 1975; Martin et al., 1976): this is well shown in *Case* 3, where the level fell below 2·5 µg/l after surgery and has remained low as the patient has remained clinically free of tumour. Failure of an elevated CEA to fall after resection is



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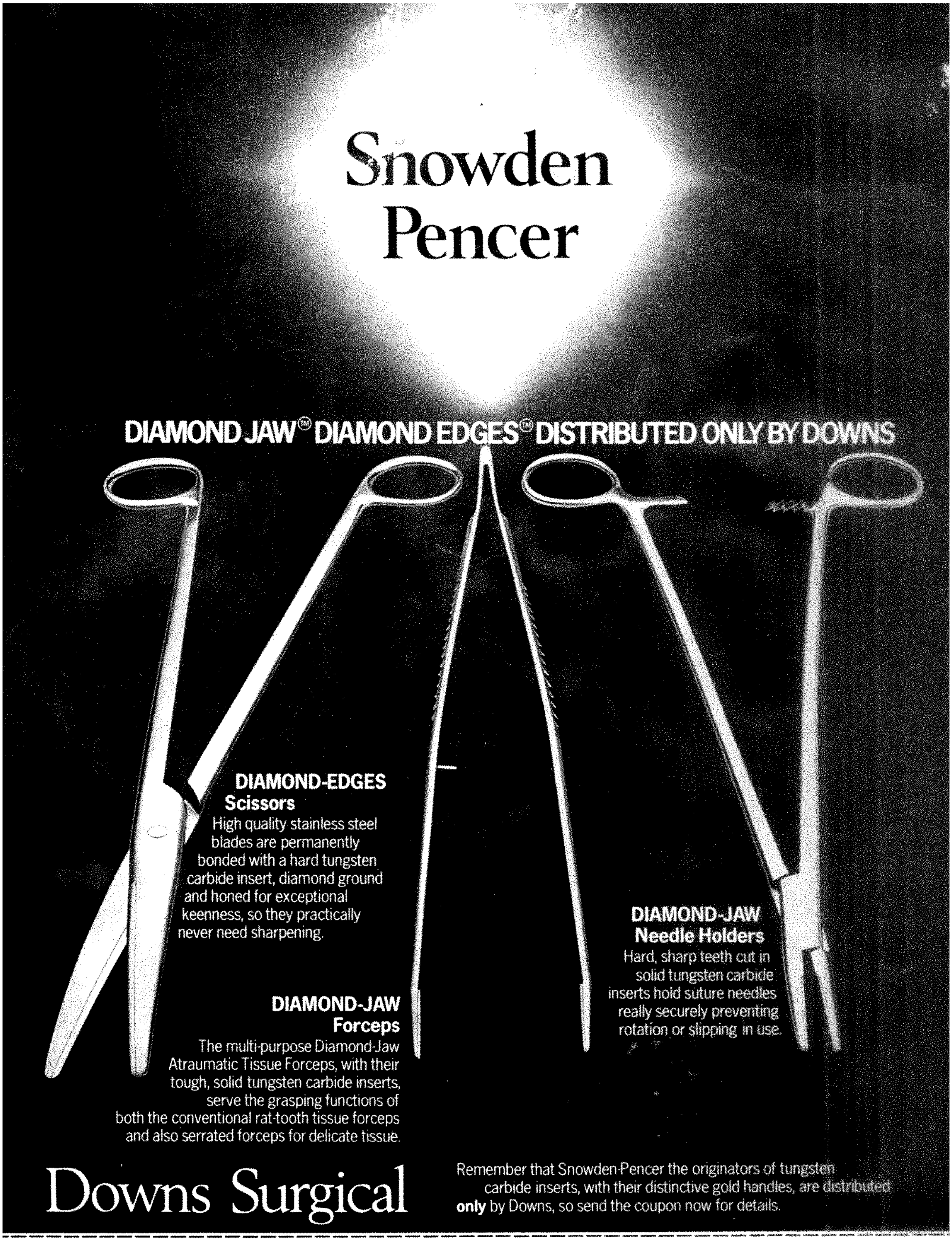

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indicative of incomplete excision or recurrence; this is seen in *Case* 2, where a persistently elevated CEA was found in the presence of a second or recurrent colonic cancer. Removal of the residual cancer resulted in the CEA level returning to normal. In *Case* 1 we see the effect of removing a bulky tumour, with CEA falling to near normal levels, only to rise as the disease progresses. Several authors (Dhar et al., 1972; Zamcheck, 1975; Martin et al., 1976) have reported CEA elevation in patients with recurrent cancer before any other clinical investigation revealed tumour, and the development of a rising CEA after apparent curative surgery now provides good grounds for a 'second look' operation, even when all other investigations are normal. This is illustrated well by *Case* 4, where the CEA level increased and remained elevated as the result of a solitary hepatic metastasis which was undetected by other investigations for over 1 year. The correlation of CEA and the response to chemotherapy has also been investigated (Skarin et al., 1974); changes in CEA levels correspond well to progression or regression of the disease. The serial assay of CEA also appears to be useful in the management of some non-gastrointestinal tract tumours, including breast and gynaecological tumours (Stewart et al., 1974; DiSaia et al., 1977).

CEA has been thoroughly evaluated over the past 10 years and its place in clinical practice can now be defined. Measurement of this antigen has little to offer in the detection of malignant disease, but a pre-treatment estimation with serial follow-up provides good estimation of the completeness of excision or effectiveness of therapy. A persistently high or rising level indicates progression of the cancer. A rising post-operative CEA level is a good indication for a 'second look' procedure.

Acknowledgement

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References

ABELEV G. J. (1974) α-Fetoprotein as a marker of embyro-specific differentiation in normal and tumor tissues. *Transplant. Rev.* **20**, 3–37.

ASTLER V. B. and COLLER F. A. (1954) The prognostic significance of direct extension of carcinoma of the colon and rectum. *Ann. Surg.* **139**, 846–852.

BULLEN A. W., LOSOWSKY M. S., CARTER S. et al. (1977) Diagnostic usefulness of plasma carcinoembryonic antigen levels in acute and chronic liver disease. *Gastroenterology* **73**, 673–678.

CONCANNON J. P., DALBOW M. H. and FRICK J. C. (1973) Carcinoembryonic antigen plasma levels in untreated cancer patients and patients with metastatic disease. *Radiology* **108**, 191–193.

CONCANNON J. P., DALBOW M. H., LIEBLER G. A. et al. (1974) The carcinoembryonic antigen assay in bronchogenic carcinoma. *Cancer* **34**, 184–192.

DHAR P., MOORE T., ZAMCHECK N. et al. (1972) Carcinoembryonic antigen (CEA) in colonic cancer. Use in preoperative and postoperative diagnosis and prognosis. *JAMA* **221**, 31–35.

DILWARI J. B., PHILIPPAKOS D., BLENDIS L. M. et al. (1975) Carcinoembryonic antigen in differential diagnosis of carcinoma of pancreas from chronic pancreatitis. *Br. Med. J.* **1**, 668.

DISAIA P. J., MORROW C. P., HAVERBACK J. et al. (1977) Carcinoembryonic antigen in cancer of the female reproductive system. *Cancer* **39**, 2365–2370.

DOOS W. G., WOLFF W. I., SHINYA H. et al. (1975) CEA levels in patients with colorectal polyps. *Cancer* **36**, 1996–2003.

GELDER F. B., REESE C. J., MOOSSA A. R. et al. (1978) Purification, partial characterization, and clinical evaluation of a pancreatic oncofetal antigen. *Cancer Res.* **38**, 313–324.

GOLD P. and FREEDMAN S. O. (1965) Demonstration of tumour-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. *J. Exp. Med.* **121**, 439–462.

HANSEN H. J., LANCE K. P. and KRUPEY J. (1971) Demonstration of an ion sensitive antigenic site on carcinoembryonic antigen using zirconyl phosphate. *Clin. Res.* **19**, 143.

KHOO S. K. and MACKAY I. R. (1973) Carcinoembryonic antigen in serum in diseases of the liver and pancreas. *J. Clin. Pathol.* **26**, 470–475.

MARTIN E. W., JAMES K. K., HURTUBISE P. E. et al. (1977) The use of CEA as an early indicator for gastrointestinal tumor recurrence and second-look procedures. *Cancer* **39**, 440–446.

MARTIN E. W., KIBBEY W. E., DIVECCHIA L. et al. (1976) Carcinoembryonic antigen. Clinical and historical aspects. *Cancer* **37**, 62–81.

NUGENT F. W. and HANSEN E. R. (1971) Radio-immunoassay of carcinoembryonic antigen as a diagnostic test for cancer of the colon: a preliminary. *Lahey Clin. Found. Bull.* **20**, 85–88.

ROCHE DIAGNOSTICS (1976) *Procedure Manual for CEA–Roche Carcinoembryonic Antigen Assay*. Nutley, New Jersey.

SKARIN A. T., DELWICHE R., ZAMCHECK N. et al. (1974) Carcinoembryonic antigen: clinical correlation with chemotherapy for metastatic gastrointestinal cancer. *Cancer* **33**, 1239–1245.

STEWART A. M., NIXON D., ZAMCHECK N. et al. (1974) Carcinoembryonic antigen in breast cancer patients: serum levels and disease progress. *Cancer* **33**, 1246–1252.

SUGARBAKER P. H., ZAMCHECK N. and MOORE F. D. (1976) Assessment of serial carcinoembryonic antigen (CEA) assays in postoperative detection of recurrent colorectal cancer. *Cancer* **38**, 2310–2315.

THOMPSON D., KRUPEY J., FREEDMAN S. O. et al. (1969) The radioimmunoassay of circulating carcinoembryonic antigen of the human digestive system. *Proc. Natl Acad. Sci.* **64**, 161–167.

WOOD R. A. B. and MOOSSA A. R. (1977) The prospective evaluation of tumor associated antigens for the early diagnosis of pancreatic cancer. *Br. J. Surg.* **64**, 718–720.

VECCHIO T. J. (1966) Predictive value of a single diagnostic test in unselected populations. *N. Engl. J. Med.* **274**, 1171–1173.

ZAMCHECK N. (1975) The present status of CEA in diagnosis, prognosis, and evaluation of therapy. *Cancer* **36**, 2460–2468.

ZAMCHECK N., MOORE T., DHAR P. et al. (1972) Immunologic diagnosis and prognosis of human digestive tract cancer. Carcinoembryonic antigens. *N. Engl. J. Med.* **286**, 83–86.

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Arterial obstruction of the upper limb in Buerger's disease: its incidence and primary lesion

MASAFUMI HIRAI AND SHIGEHIKO SHIONOYA*

SUMMARY

In the present study, the incidence of upper extremity involvement and the primary lesion of the arm in Buerger's disease were investigated with special regard to arteriographic findings in the upper limb. Of 34 patients with Buerger's disease admitted to our hospital during the 12-month period from March 1977 to February 1978, in 31 cases (91 per cent) the existence of arterial obstruction of the upper limb was confirmed. From the results of arteriographic study in 78 arms, the primary lesion of Buerger's disease appears to develop most frequently in the digital arteries. However, it is possible for the disease to develop independently in the arteries of the hand, or in the radial or ulnar artery. Although the aetiology of Buerger's disease is not definitely known, it is suggested that repeated blunt injury to the hand or fingers is involved in the evolution of the disease as well as in the appearance of symptoms.

In Buerger's disease, arterial obstruction may occur not only in the leg but also in the arm, and the presence of upper extremity involvement has been used as one of the criteria for differentiation of this disease from arteriosclerosis obliterans (Barker, 1962; McKusick et al., 1962; McPherson et al., 1963; Szilagyi et al., 1964; Goodman et al., 1965; Thieme et al., 1965; Mozes et al., 1970; Morris-Jones and Jones, 1973). The incidence of blood flow disturbance of the upper limb in Buerger's disease has been reported to be from 14 to 100 per cent (*Table I*). It is considered that this great variance in the reported incidence can be attributed to the different criteria used for the diagnosis of Buerger's disease and also to the different methods used for confirmation of an occlusive lesion. Various methods have been used for diagnosis of arterial obstruction (Coffman and Cohen, 1971; Henderson and Hackett, 1978; Hirai, 1978), but no method is superior to arteriography as a diagnostic aid for accurate confirmation of the obstruction.

In the present study, in order to determine the precise incidence of arterial obstruction of the upper limb in Buerger's disease, arteriography was employed in both symptomatic and asymptomatic limbs in cases diagnosed clinically as having Buerger's disease. Furthermore, development of the primary lesion of Buerger's disease and its evolution were investigated on the basis of arteriographic findings.

Table I: INCIDENCE OF UPPER EXTREMITY INVOLVEMENT IN BUERGER'S DISEASE

Author	Year	No. of cases studied	No. of cases with upper limb involvement
Szilagyi et al.	1964	22	3 (14)
Inada and Katsumura	1972	206	32 (16)
Kummer et al.	1977	36	8 (22)
Ishikawa et al.	1962	96	36 (38)
Shionoya et al.	1974	100	42 (42)
Schatz et al.	1966	41	22 (54)
McKusick et al.	1962	28	17 (61)
Hill et al.	1973	106	68 (64)
Goodman et al.	1965	80	59 (74)
Mozes et al.	1970	22	17 (77)
McPherson et al.	1963	45	45 (100)

Figures in parentheses are percentages.

Patients and methods

During the 12-month period from March 1977 to February 1978, 34 patients with Buerger's disease were admitted to the Department of Surgery, Nagoya University Branch Hospital. In these patients, the presence of arterial obstruction of the upper limb was investigated by means of brachial arteriography, clinical findings and determination of digital blood pressure (Hirai, 1978). The diagnosis of Buerger's disease was based on the criteria described in previous papers (Shionoya et al., 1974; Hirai and Shionoya, 1978). In all patients studies were made of complete blood count, urinalysis, fasting blood sugar and serum cholesterol and chest X-rays and electrocardiograms were taken. In addition to clinical assessment femoral arteriography, which was carried out in 31 of 34 patients, was reviewed.

All patients were male and at the onset of their symptoms all were smokers. The initial symptoms of vascular disease appeared at a mean age of 36 years, with a range of 25–48 years. Only 2 patients were over 45 years at the first onset of symptoms. The mean duration from the onset of the disease to the time of this investigation was 6·5 years, with a range of 2 months to 23 years. All the patients were otherwise in good health and had no evidence of organic heart disease, arterial aneurysm, diabetes mellitus, radiographically demonstrable calcification of peripheral arteries or scleroderma. All the patients had normal blood cholesterol levels.

Superficial thrombophlebitis had occurred in 20 patients and 17 patients complained of intermittent claudication in the foot (Hirai and Shionoya, 1978). Involvement of the upper extremity was observed in 22 patients. It was confirmed by signs of digital ischaemia, such as cyanosis or gangrene, as well as by the absence of pulsation in the radial or ulnar artery in association with a positive Allen test (Allen, 1929). Thirty-one patients had at least one of these three manifestations. Twenty-seven patients had a history of or evidence of skin ulceration on the toes or fingers. Blood pressure measurement at the second toe (Hirai and Shionoya, 1978) revealed a significantly low blood pressure in at least one leg of all the patients, and arterial occlusion in the leg was confirmed by femoral arteriography in 31 patients. On arteriography the arteries proximal to the occlusion sites were seen to be regular and smooth. No intimal plaques or calcifications were visible.

Brachial arteriography was carried out in 30 of 34 patients. Retrograde puncture of the brachial artery was performed in the antecubital fossa and 15 ml of contrast medium (60 per cent of Conray) were injected rapidly by hand or automatic injector. Twenty films were exposed over a period of at least 15 s. The usual rate was 1 film per second.

To investigate the development of the primary lesion in Buerger's disease, arteriographic findings in a total of 78 limbs were studied, including 33 limbs in 24 patients undergoing brachial arteriography at our hospital before February 1977 and 45 limbs in 27 patients after March 1977.

Results

Incidence

In 31 of 34 patients (91 per cent) arterial obstruction in at least one upper limb was confirmed. In 27 of

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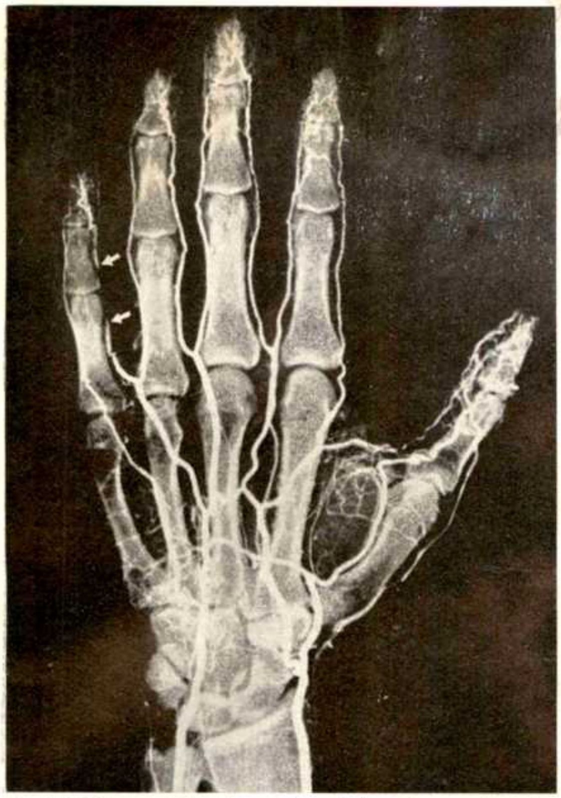

Fig. 1. A 37-year-old patient with no ischaemic symptoms in the hands. Right brachial arteriogram shows segmental occlusion of the lateral digital artery in the little finger. In the other digital arteries, remarked tortuosity is observed.

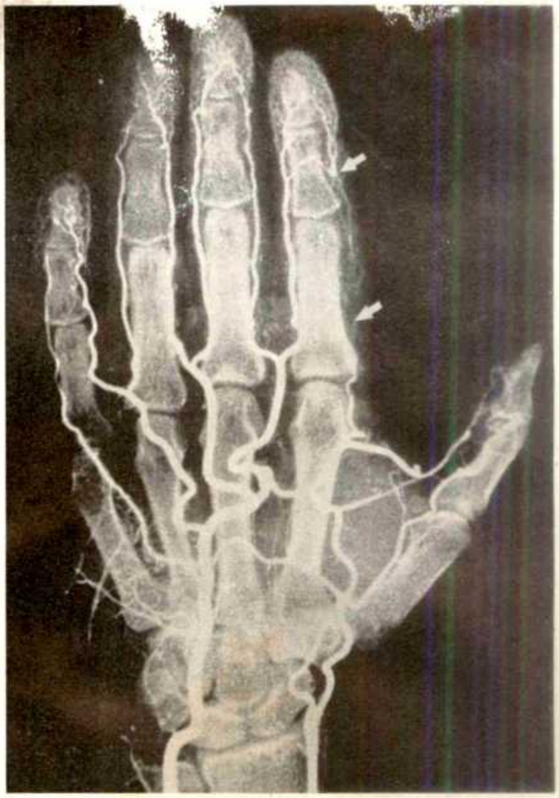

Fig. 2. A 49-year-old patient with no ischaemic symptoms in the hands. Right brachial arteriogram shows occlusion of the lateral digital artery of the index finger.

these 31 cases arterial obstruction was detected by arteriography; in the remaining 4 cases it was confirmed by the presence of definitive signs of ischaemia, such as cyanosis or gangrene, as well as by the absence of wrist pulsations in association with a positive Allen test and a decreased digital pressure. In 3 other cases arteriography, which was performed in both arms, failed to reveal arterial obstruction.

Of 27 cases shown by arteriography to have arterial obstruction, 26 underwent bilateral arteriography. In 8 of these 26 cases obstruction was found on one side only, with no obvious arterial obstruction on the opposite side. An inspection of the site of obstruction in these 8 cases revealed that 5 cases had obstruction of the digital artery, 2 of the ulnar artery and 1 of the radial artery.

Arteriographic findings

Seventy-eight limbs were submitted to brachial arteriography (*Table II*). Thirty-three of these investigations were carried out before February 1977, being performed mainly in patients with severe digital ischaemia. During this period, obstruction of both the radial and ulnar artery was overwhelmingly prevalent. The remaining arteriograms (45), performed from March 1977 onwards, were carried out irrespective of whether or not there were symptoms or signs in the arm. In this group, obstruction of the more distal arteries was detected with increased frequency. In 39 hands without clinical evidence of ischaemic disease the most common site of occlusion was the digital artery (*Figs*. 1, 2).

Table II: THE SITE OF ARTERIAL OCCLUSION IN 78 ARMS

	April 1967–February 1977 ($n = 33$)		
Involved artery	Ischaemic symptoms	No symptoms	Total
Radial and ulnar	15	2	17 (52)
Radial only	0	0	0
Ulnar only	4	2	6 (18)
Hand*	5	2	7 (21)
Digital	2	1	3 (9)
	March 1977–February 1978 ($n = 45$)		
Involved artery	Ischaemic symptoms	No symptoms	Total
Radial and ulnar	5	0	5 (11)
Radial only	1	0	1 (2)
Ulnar only	7	13	20 (44)
Hand*	0	3	3 (7)
Digital	0	16	16 (36)

* Hand arteries included deep or superficial palmar arch, common digital artery, metacarpal artery and princeps pollicis artery.

Figures in parentheses are percentages.

By further studying the arteriographic findings in individual cases with involvement of the digital artery, it was found that in some cases the whole length of the

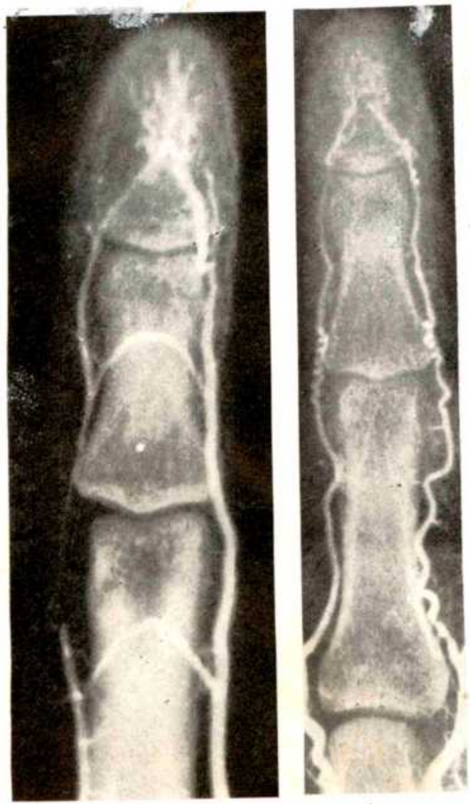

Fig. 3. Segmental occlusion (*a*) and tortuosity (*b*) of the digital artery adjacent to the interphalangeal joint.

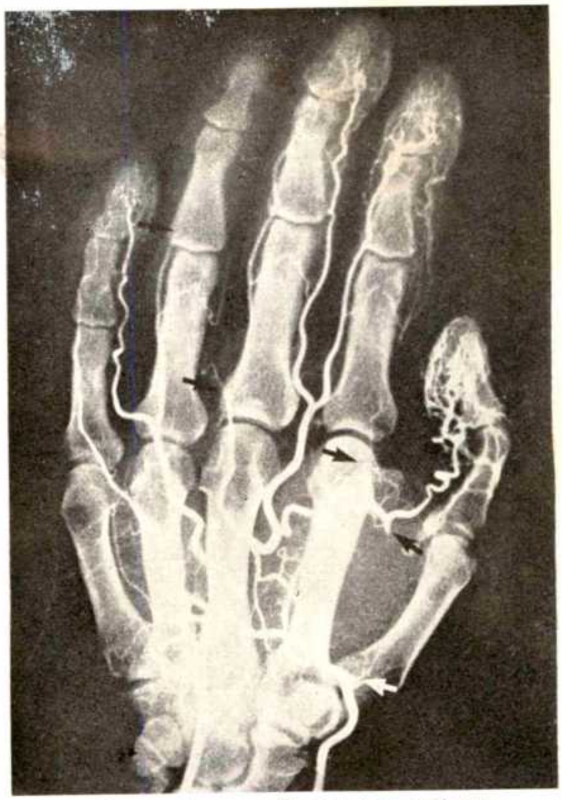

Fig. 4. A 42-year-old patient. The arteriogram shows segmental occlusion of the princeps pollicis artery, complete occlusion of the lateral digital artery of the index finger and occlusion of the lateral digital artery at its origin and the medial digital artery at the proximal interphalangeal joint of the ring finger.

artery was involved and only the distal part in others. In addition, segmental occlusive lesions of the digital artery were observed (*Figs*. 1–3). The segmental type of obstruction accounted for 36 per cent of cases in which occlusive lesions were detected only in the digital artery. Frequently, this type of occlusion was observed adjacent to the interphalangeal joint. In addition to obstructive lesions, the digital artery sometimes exhibited tortuosity. This was observed in 56 per cent of cases. There were relatively large tortuosities and also fine ones. It was noted that fine tortuosity was often seen adjacent to the interphalangeal joints, as were the segmental occlusive lesions (*Fig*. 3).

With regard to the arteries of the hand, such as the deep or superficial palmar arches, common digital artery, metacarpal artery or princeps pollicis artery, diffuse occlusion associated with an involved radial or ulnar artery was a common finding. However, segmental occlusive lesions were also observed in this area (*Figs*. 4, 5). Lesions of the radial and ulnar arteries included obstruction involving the whole length of the artery, segmental obstruction and irregularities that were often seen adjacent to the wrist joint (*Figs*. 5, 6). Other than these, in 4 cases findings similar to those of hypothenar hammer syndrome (Conn et al., 1970; Benedict et al., 1974) were encountered, i.e. localized lesions of the ulnar artery were detected near the hook of the hamate bone (*Fig*. 7). In these patients no history of blunt trauma to the palm which might have caused hypothenar hammer syndrome was obtained. In all but one of 59 cases that were found to have obstructions in the arteries of the hand, or in the radial or ulnar artery, occlusive lesions of the digital artery were also observed. In an exceptional case, which showed obstruction involving the whole length of the ulnar artery, no clear evidence of obstruction was seen in the other arteries, including the digital artery.

Discussion

The incidence of upper extremity involvement in Buerger's disease has been reported as from 14 to 100 per cent (*Table I*). This great variance among investigators might be explained mainly by the different criteria used for the diagnosis of Buerger's disease and the different methods used for confirmation of an occlusive lesion. McPherson et al. (1963), who reported an incidence of 100 per cent, considered that the presence of an occlusive lesion in the upper limb was an essential requirement for a diagnosis of Buerger's disease. Mozes et al. (1970), who reported the next highest incidence (77 per cent), diagnosed Buerger's disease clinically if any two of three manifestations, i.e. upper extremity involvement, superficial thrombophlebitis or Raynaud's phenomenon, were seen. Naturally, the incidence becomes high if such diagnostic criteria are employed. In the present study

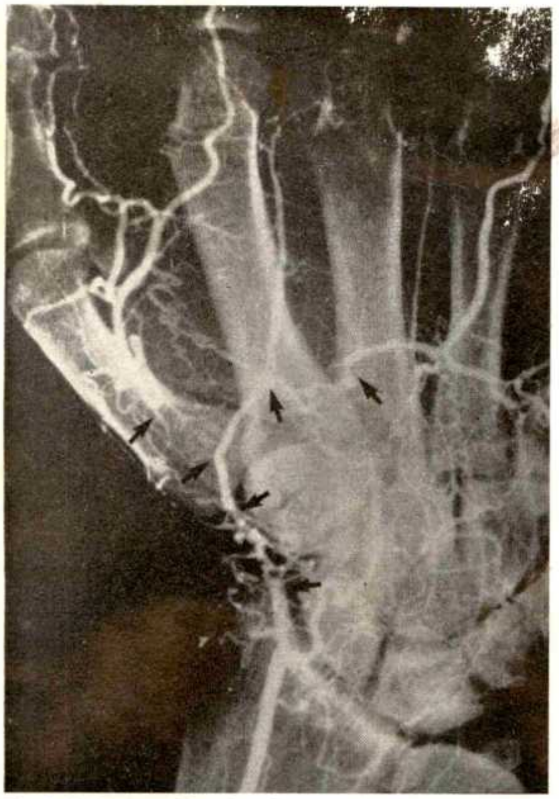

Fig. 5. A 51-year-old patient. Segmental occlusions are seen in the radial artery, deep palmar arch and princeps pollicis artery. The ulnar artery is completely occluded.

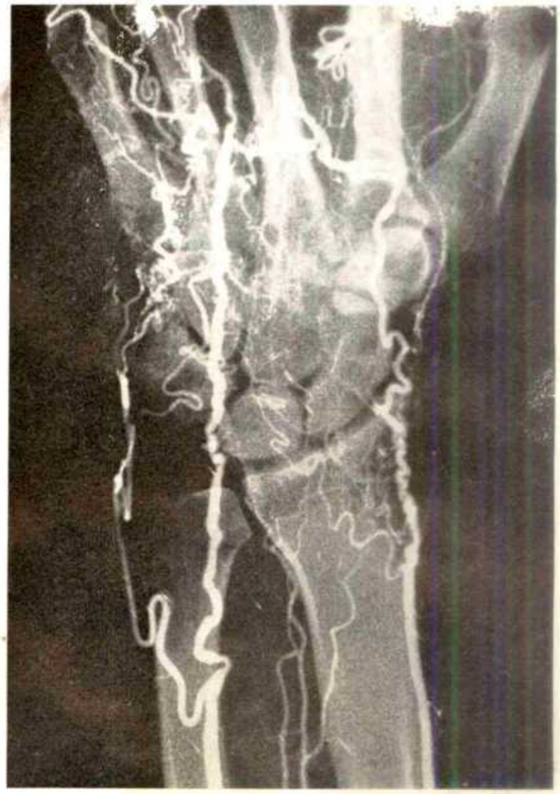

Fig. 6. A 46-year-old patient. Severe irregularities are observed in the radial and ulnar arteries adjacent to the wrist.

Buerger's disease was diagnosed on the basis not only of the presence of upper extremity involvement, but also on smoking habit, male sex, comparative youth and coexistence of thrombophlebitis or foot claudication, in the absence of findings suggesting other diseases. Furthermore, arteriographic findings were also considered. These criteria for the diagnosis of Buerger's disease have been widely used by other authors (Barker, 1962; McKusick et al., 1962; Szilagyi et al., 1964; Goodman et al., 1965; Thieme et al., 1965; Schatz et al., 1966; Eastcott, 1969; Inada and Katsumura, 1972; Kummer et al., 1977).

Goodman et al. (1965) reported a 74 per cent incidence of upper extremity involvement in Buerger's disease and commented that their high incidence was not exceptional, it was merely a reflection of their prime concern to determine the frequency of the disease. In our present study, only 6 of 34 patients were admitted to hospital complaining of symptoms of blood flow disturbance in the upper limb either associated with lower limb symptoms or alone. None the less, careful clinical questioning and physical examination revealed that 22 cases had arterial occlusion in the upper limb. Therefore, if the fact that arterial occlusion may occur in the arm as well as in the leg is always taken into account whenever physicians see patients, arterial obstruction of the upper limb can be detected with increased frequency. In our present study, however, in which, since March 1977, arteriography was carried out regardless of the absence of clinical evidence of the disease, arterial

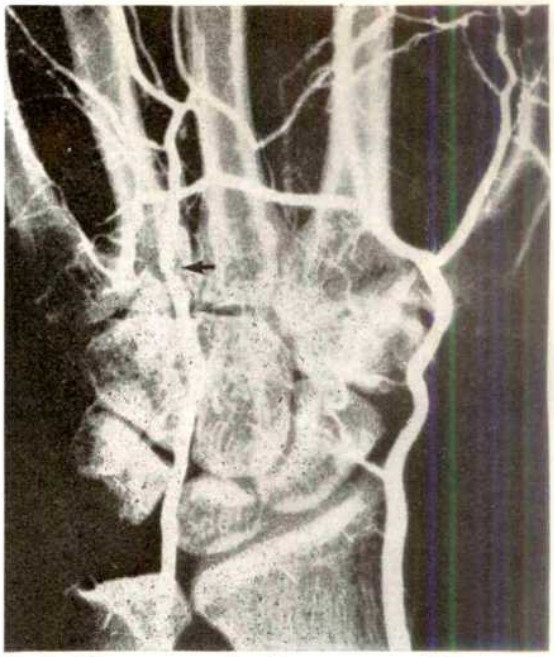

Fig. 7. A 36-year-old patient. Severe stenosis of the ulnar artery is observed near the hook of the hamate bone. This patient had no history of blunt trauma to the palm.

obstruction of the upper limb was found to be present in 91 per cent of the cases. These findings indicate that an arterial occlusive lesion does not always produce ischaemic signs in the limbs (Holstein and Sager, 1973; Hirai and Shionoya, 1976). However, the fact that arterial lesions of the upper limb can be seen in an extremely high percentage of patients is of great importance in advising the patients, as described below.

Regarding the results of arteriographic studies before February 1977, when arteriography was performed mainly in patients with severe digital ischaemia, occlusion of both the radial and ulnar arteries was the most frequent finding. From the analysis of arteriographic findings in advanced cases, it appears that the primary lesion of the upper limb in Buerger's disease frequently occurs in the radial or ulnar artery. However, obstruction of the more distal arteries was detected with increased frequency after March 1977. In cases without clinical evidence of ischaemic disease, the most common site of occlusion was the digital artery. Moreover, in cases with arterial occlusion in the arteries of the hand, the radial or the ulnar artery, an association with obstruction of the digital artery was observed in all but one case. From these findings, it might be considered that the primary lesion of Buerger's disease develops most frequently in the digital artery (Kamiya, 1964; Goodman et al., 1965).

The pattern of obstruction of the digital artery was studied and segmental obstruction was seen in 36 per cent of cases, indicating that the primary lesion in the digital artery does not always develop at the tip of the fingers. In addition, the fact that segmental occlusions are observed in the arteries of the hand and in the radial and ulnar arteries suggests that Buerger's disease can develop not only in the fingers but also in these parts independently.

The real aetiology of Buerger's disease is still unknown. It is assumed, however, that repeated blunt injury to the hand or fingers may be involved in the development of the disease, as well as in the appearance and exacerbation of its symptoms (McKusick et al., 1962). Development of obstruction, irregularity and tortuosity in the area adjacent to the joint all suggest that repeated joint movement constitutes one of the factors responsible for evolution of the disease. Furthermore, it was recognized by taking a detailed history that in two patients in our series digital ischaemic signs developed after using their hands for several months at their jobs. In ulnar arterial disease resembling hypothenar hammer syndrome, it appears that mild blunt trauma to the palm, which exerts no influence in normal subjects, may play a role in the development of this lesion in the presence of underlying Buerger's disease.

The above-described arteriographic findings are not considered to be necessarily specific for Buerger's disease, since we observed segmental obstruction, tortuosity of the digital arteries and disease of the ulnar artery near the hook of the hamate bone in arteriosclerosis obliterans and Raynaud's phenomenon. None the less, since arterial obstruction of the upper limb occurs in a high percentage of patients with Buerger's disease, it is recommended that injuries to the hand or fingers through occupation, sport, hobby or habits should be avoided as much as possible in all [illegible] Buerger's disease, in addition to cessa[illegible] (Goodman et al., 1965; Schatz et al., [illegible], 1970; Kummer et al., 1977) and [illegible] exposure of the hand to cold (McKusick et al., 1962; Hill et al., 1973).

References

ALLEN E. V. (1929) Thromboangiitis obliterans: method of diagnosis of chronic occlusive arterial lesions distal to the wrist with illustrative cases. *Am. J. Med. Sci.* **178**, 237–244.

BARKER N. W. (1962) The case for retention of the diagnostic category 'thromboangiitis obliterans'. *Circulation* **25**, 1–4.

BENEDICT K. T., CHANG W. and MCCREADY F. J. (1974) The hypothenar hammer syndrome. *Radiology* **111**, 57–60.

COFFMAN J. D. and COHEN A. S. (1971) Total and capillary fingertip blood flow in Raynaud's phenomenon. *N. Engl. J. Med.* **285**, 259–263.

CONN J., BERGAN J. J. and BELL J. L. (1970) Hypothenar hammer syndrome: post-traumatic digital ischemia. *Surgery* **68**, 1122–1128.

EASTCOTT H. H. G. (1969) *Arterial Surgery*. London, Pitman, pp. 96–112.

GOODMAN R. M., ELIAN B., MOZES M. et al. (1965) Buerger's disease in Israel. *Am. J. Med.* **39**, 601–615.

HENDERSON H. P. and HACKETT M. E. J. (1978) The value of thermography in peripheral vascular disease. *Angiology* **29**, 65–75.

HILL G. L., MOELIONO J., TUMEWU F. et al. (1973) The Buerger syndrome in Java. *Br. J. Surg.* **60**, 606–613.

HIRAI M. (1978) Arterial insufficiency of the hand evaluated by digital blood pressure and arteriographic findings. *Circulation* **58**, 902–908.

HIRAI M. and SHIONOYA S. (1976) Progression of arterial occlusion in Buerger's disease. *Folia Angiol.* **26**, 281–285.

HIRAI M. AND SHIONOYA S. (1978) Intermittent claudication in the foot and Buerger's disease. *Br. J. Surg.* **65**, 3–8.

HOLSTEIN P. and SAGER P. (1973) Toe blood pressure in peripheral arterial disease. *Acta Orthop. Scand.* **44**, 564–572.

INADA K. and KATSUMURA T. (1972) The entity of Buerger's disease. *Angiology* **23**, 668–682.

ISHIKAWA K., KAWASE S. and MISHIMA Y. (1962) Occlusive arterial disease in extremities, with special reference to Buerger's disease. *Angiology* **13**, 398–411.

KAMIYA K. (1964) Buerger's disease. *J. Vasc. Dis.* **1**, 186–202.

KUMMER A., WIDMER L. K., DASILVA A. et al. (1977) Thromboangiitis obliterans zum Morbus Winiwarter-Bürger. *VASA* **6**, 384–391.

MCKUSICK V. A., HARRIS W. S., OTTESEN O. E. et al. (1962) Buerger's disease: a distinct clinical and pathologic entity. *JAMA* **181**, 5–12.

MCPHERSON J. R., JUERGENS J. L. and GIFFORD R. W. (1963) Thromboangiitis obliterans and arteriosclerosis obliterans. Clinical and prognostic differences. *Am. Int. Med.* **59**, 288–296.

MORRIS-JONES W. and JONES C. D. P. (1973) Buerger's disease in women. *Angiology* **24**, 675–690.

MOZES M., CHAANSKY G , DOITSCH V. et al. (1970) The association of atherosclerosis and Buerger's disease: a clinical and radiological study. *J. Cardiovasc. Surg.* **11**, 52–59.

SCHATZ I. J., FINE G. and EYLER W. R. (1966) Thromboangiitis obliterans. *Br. Heart J.* **28**, 84–91.

SHIONOYA S., BAN I., NAKATA Y. et al. (1974) Diagnosis, pathology, and treatment of Buerger's disease. *Surgery* **75**, 695–700.

STRICHT J. V. D., GOLDSTEIN M., FLAMAND J. P. et al. (1970) Evolution and prognosis of thromboangiitis obliterans. *J. Cardiovasc. Surg.* **14**, 9–16.

SZILAGYI D. E., DERUSSO F. J. and ELLIOTT J. P. (1964) Thromboangiitis obliterans. *Arch. Surg.* **88**, 824–835.

THIEME W. T., STRANDNESS D. E. and BELL J. W. (1965) Buerger's disease. Further support for the entity. *Northwest Med.* **64**, 264–268.

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Late revascularization of the lower limb following acute arterial occlusion

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SUMMARY

Thirty-four patients presenting with signs of grave ischaemia of the lower limb following acute arterial occlusion had revascularization procedures performed. Fifteen of the incidents followed embolism or thrombosis and 19 were due to a traumatic cause.

Limb salvage was achieved in 67 per cent of the non-traumatic group and in 56 per cent of the traumatic group. Severe complications such as crush syndrome and disseminated intravascular coagulation occurred but there were no deaths.

No significant adverse factors with regard to limb prognosis could be defined.

We feel that late revascularization in the absence of major gangrene is worth while provided that facilities for critical postoperative care exist.

IRREVERSIBLE limb ischaemia following acute arterial occlusion is difficult to define. Whether to revascularize or not may severely tax clinical judgement, because the consequences of re-establishing circulation in a dead limb may be life-threatening. By the same token, major amputation of a viable limb is undesirable. We report our experience of revascularization of the lower limb in the presence of grave ischaemia. All results have been assessed over a period of 3 months to 3 years.

Patients

During a 3-year period, 34 patients presented after major acute arterial occlusion with clinical signs often regarded as indicating irreversible ischaemia. These signs, present in all patients, were an 'ice-cold' limb with skin mottling, anaesthesia and total muscle paralysis. In addition, 16 patients (47 per cent) presented with significant muscle rigidity involving one or more fascial compartments.

The patients' ages ranged from 8 to 75 years (mean 31 years) and 25 were males. Non-traumatic acute arterial occlusion occurred in 15 patients, due to embolism (8) or thrombosis (7). The source of the embolus was the left atrium in 2 patients with atrial fibrillation, a cardiac mural thrombus in 5 patients with ischaemic heart disease and a grossly dilated ventricle in 1 patient with cardiomyopathy. The delay before presentation to hospital ranged from 4 h to 10 days (mean 8 days).

The sites of arterial obstruction were the femoropopliteal segment (8), the aortic bifurcation (4), the iliac artery (1), the popliteal artery (1) and distal vessels (1).

Associated diseases in 10 patients included hypertension (2), congestive heart failure (4), cerebrovascular disease (2) and diabetes (2).

Nineteen patients with acute arterial occlusion complicating penetrating (4) or blunt (15) trauma presented 4–72 h after injury (mean 24 h). There was partial vessel wall disruption in 4 patients, total disruption in 6 and thrombosis in 9.

The vessels involved were the popliteal (10), superficial femoral (8) and the iliac (1) arteries.

Associated injuries included long bone fractures or dislocations in 14 patients, severe head injury in 3 patients and a penetrating abdominal wound in 1 patient.

Management and results (*Table I*)

Non-traumatic group

Balloon catheter embolectomy via the femoral route was performed in all cases.

Regional heparin was routinely infused in a concentration of 10 000 units of heparin per litre of isotonic saline. Systemic heparin was administered for at least 7 days after the operation. In addition, when the cardiac status permitted LMW dextran (Rheomacrodex) was infused at the rate of 500 ml per 12 h, for 36 h.

Thirteen patients had open two-compartment fasciotomy from knee to ankle on the medial side and along the full length of the extensor compartment.

Limb salvage was achieved in 10 patients (67 per cent), of whom 9 are ambulant. Return of pedal pulses was noted in 7 patients. One patient developed intermittent claudication 6 months after operation.

Amputation within 48 h was necessary in 5 patients (33 per cent), below-knee in 2 and mid-thigh in 3. In at least 1 patient revascularization permitted a more distal amputation. Two patients developed foot drop due to extensor compartment infarction.

One patient with atrial fibrillation developed paraplegia, with a sensory level at L1, despite restoration of all peripheral pulses. No sign of recovery is evident 6 months after operation. Postoperatively this patient developed iliac vein thrombosis despite heparin administration and survived two episodes of major pulmonary embolism. Inferior vena caval interruption was eventually performed.

Traumatic group

Nineteen patients with arterial injuries were treated by vein grafts (15), end-to-end arterial repair (2), lateral suture (1) and thrombectomy with vein patch angioplasty (1). Regional heparinization and balloon catheter thrombectomy were routinely employed.

All patients received an intravenous fluid load and 10 g of mannitol intraoperatively. Broad spectrum antibiotics were administered in all cases. Open fasciotomy was performed in 17 cases.

Orthopaedic injuries were treated on their merits in 14 patients, mainly by external fixation. Craniotomy was necessary in 2 patients and laparotomy in 1 patient.

One patient died due to a head injury within 24 h of operation and has been excluded from further analysis.

Limb salvage was achieved in 10 patients (56 per cent). Nine patients are ambulant. Severe causalgia precludes ambulation in 1 patient. Peripheral pulses have been restored in 7 patients.

Major amputation became necessary in 8 patients (44 per cent), below-knee in 3 and mid-thigh in 5. Five amputations were necessary within 48 h of operation owing to failure of the arterial repair. Three patients required amputation within 7 days. The indications were sepsis, with massive secondary haemorrhage from the arterial repair, necessitating a major vessel ligation in 2 patients and severe rest pain

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Table I: RESULTS OF LATE REVASCULARIZATION OF THE LOWER LIMB FOLLOWING ACUTE ARTERIAL OCCLUSION

Aetiology	Total no. cases	Mortality	Amputation Major	Amputation Minor	Limb salvage	Ambulant	Pulses	Claudication
Embolism and thrombosis	15	0	5 (33·3)	0	10 (66·7)	9 (60)	7 (66·7)	1 (6·7)
Traumatic	18*	0*	8 (44·4)	2 (6·1)	10 (55·6)	9 (50)	7 (38·9)	0
Total	33	1 (3·0)	13 (39·4)	2 (6·1)	20 (60·6)	18 (54·5)	14 (42·4)	1 (3·0)

* Excludes 1 death occurring during the first 24 h (cerebral injury).
Figures in parentheses are percentages.

Table II: COMPLICATIONS OF LATE REVASCULARIZATION OF THE LOWER LIMB FOLLOWING ACUTE ARTERIAL OCCLUSION

Aetiology	Total	Crush syndrome	DIC	Massive secondary haemorrhage	Extensor compartment infarction	Oedema	Causalgia	Osteitis	Ischaemic myelopathy	Major pulmonary embolus
Embolism and thrombosis	15	0	0	0	2 (13·3)	0	0	0	1 (6·7)	1 (6·7)
Traumatic	18*	2 (11·1)	1 (5·6)	2 (11·1)	3 (16·7)	1 (5·6)	1 (5·6)	1 (5·6)	0	0
Total	33	2 (6·1)	1 (3·0)	2 (6·1)	5 (15·2)	1 (3·0)	1 (3·0)	1 (3·0)	1 (3·0)	1 (3·0)

* Excludes 1 death occurring during the first 24 h (cerebral injury).
Figures in parentheses are percentages.
DIC, Disseminated intravascular coagulation.

Table III: COMPARISON OF CLINICAL FEATURES IN LIMB SALVAGE GROUP AND MAJOR AMPUTEES

			Site of obstruction					Clinical signs				
	Mean age (yr)	Mean time interval (d)	A	I	F	P	D	'Ice-cold' with mottling	Anaesthesia	Paralysis	Significant muscle rigor	Associated fracture
Limb salvage ($n = 20$)	30·8	3·0	4 (20)	0	11 (55)	5 (25)†	0	20 (100)	20 (100)	20 (100)	7 (35)†	7 (35)†
Major amputation ($n = 13$)	29·6	3·3	0	2 (15·4)	4 (30·8)	6 (46·2)†	1 (7·7)	13 (100)	13 (100)	13 (100)	9 (69·2) †	6 (46·2)†

* n is the total number of patients, which excludes 1 death occurring during the first 24 h (cerebral injury).
Figures in parentheses are percentages.
A, Aorta; I, iliac; F, femoral; P, popliteal, D, distal.
† Difference not significant ($P > 0·05$).

in 1 patient. Transmetatarsal amputation was necessary in 2 patients for minor gangrene.

Nine patients developed additional complications (*Table II*). The crush syndrome was successfully treated by haemodialysis in 2 patients, one of whom developed disseminated intravascular coagulation.

One patient suffers causalgia 2 years after operation despite sympathectomy. Foot drop in 3 patients has been satisfactorily managed by splintage. Tibial oesteitis in 1 patient responded well to repeated local surgery. One patient has troublesome oedema.

Comparison of clinical features among limb salvage group and major amputees (Table III)

Statistical comparisons were made using χ^2 analysis ($2 \times K$ contingency table).

The two groups did not differ significantly in mean age or in respect of the average time interval between the insult and surgical treatment. However, popliteal artery occlusion was more common in major amputees (46 per cent) than in the limb salvage group (25 per cent) ($P > 0·05$), and the only patient in the series with more distal occlusion was eventually submitted to amputation.

All patients in both groups presented with an 'ice-cold' limb with skin mottling, anaesthesia and total paralysis. Rigor involving one or more muscle groups was found in 7 (35 per cent) of the limb salvage group and in 9 (69 per cent) of the major amputees. This difference just fails to attain statistical significance ($P > 0·05$).

Associated long bone fractures were present in 7 (35 per cent) of those whose limbs were salvaged and in 6 (46 per cent) of those with major amputations ($P > 0·05$).

Discussion

Although it has been shown that the limb salvage rate is decreased by an increasing time interval between the insult and surgical treatment (Martin et al., 1969; Edwards, 1973; MacGowan and Moneeram, 1973; Thompson et al., 1976), there is general agreement that revascularization should be attempted provided that the limb is viable. Assessment of viability, however, can be extremely difficult (Thompson et al., 1976). Revascularization is contraindicated with advanced muscle rigidity, but mild rigidity should not preclude the procedure (Thompson et al., 1976). Edwards (1973) suggests that revascularization may be attempted in the presence of patchy skin necrosis. Similarly, Martin et al. (1969) indicate that there is little to lose by attempting revascularization in the [redacted] frank cation (E , 1973; Thom

All lim oubtful viability. The ollowing trauma, mainly because of iated soft tissue damage with destruction aterals and increased susceptibility to infection (Robbs and Baker, 1978a, b).

At operation back-bleeding is an unreliable index of distal arterial patency as short collaterals may cause this in the presence of distal discontinuous clot (Fogarty, 1970; Provan and Ransford, 1970; Thompson et al., 1976). The only reliable method of assessment is intraoperative angiography (Fogarty, 1970; MacGowan and Moneeram, 1973; Thompson, 1974) and we have adopted this practice as a routine. The popliteal vessels may then be explored if indicated (Fogarty, 1970; Kartchner, 1972).

The administration of systemic intravenous heparin for a 7-day period has been our routine practice (Fogarty, 1970; Kartchner, 1972; MacGowan and Moneeram, 1973; Thompson et al., 1976). Long term anticoagulant therapy is reserved for patients with peripheral embolization of cardiac origin (Kartchner, 1972).

Broad spectrum antibiotic therapy is indicated for extensive soft tissue injury and in patients with open fasciotomy. We perform fasciotomy in limbs that exhibit marked tissue turgor increase initially, or if this becomes evident 24–48 h later. We prefer open two-compartment fasciotomy extending from the knee to behind and below the malleolus medially and along the full length of the extensor compartment anteriorly. Sepsis has not been a major morbidity factor, and delayed primary suture or split skin grafting has been done once the wound is healthy. This is preferable to closed fasciotomy, where areas of deep fascia may be 'skipped' leaving 'tourniquet bands'.

Almost one-third of patients in the non-traumatic group developed complications. These proved life-threatening in only 1 patient, in whom iliac vein thrombosis with repeated major pulmonary embolism occurred despite adequate heparin administration. A careful haematological study of this patient failed to reveal a hypercoagulability state.

The incidence of complications was higher following trauma, and threatened life in 25 per cent of patients. In particular, myoglobinuria with acute renal shutdown may result from extensive soft tissue trauma aggravated by ischaemia and hypotension. This complication is anticipated in this group of patients and measures are instituted to [illegible] operative diuresis. In some series an attempt has been made to render the patients alkalotic (Thompson et al., 1976). Renal failure is recognized early and treated by dialysis.

Sepsis with breakdown of arterial repair has become less of a problem since a policy of antibiotic wound lavage and delayed primary closure has been adopted (Robbs and Baker, 1977, 1978a, b).

Although not statistically significant, the pattern of results indicates that more peripheral arterial occlusions and associated fractures worsen limb prognosis. Similarly, muscle rigor was more common in patients in whom late revascularization failed.

Conclusions

In the absence of frank major gangrene we believe that revascularization should be attempted in the doubtfully viable limb following acute arterial occlusion.

However, early detection and prompt and aggressive treatment of acute renal failure, DIC and septic complications are essential if disaster is to be prevented.

Although no deaths due to complications of the operation occurred in this series, these are life-threatening and surgery should not be attempted unless facilities for critical postoperative care are available.

References

EDWARDS E. A. (1973) Acute peripheral arterial occlusion. *J. Am. Med. Assoc.* **223**, 909–912.

FOGARTY J. T. (1970) Surgical management of acute vascular occlusion. *Surg. Ann.* **2**, 207–221.

KARTCHNER M. M. (1972) Retrograde arterial embolectomy for limb salvage. *Arch. Surg.* **104**, 532–535.

MACGOWAN W. A. L. and MONEERAM R. (1973) A review of 174 patients with arterial embolism. *Br. J. Surg.* **60**, 894–898.

MARTIN P., KING R. D. and STEPHENSON C. B. S. (1969) On arterial embolization of the limbs. *Br. J. Surg.* **56**, 882–884.

PROVAN J. L. and RANSFORD A. O. (1970) The role of the Fogarty embolectomy catheter in the treatment of arterial embolism of the limbs. *Br. J. Surg.* **57**, 59–62.

ROBBS J. V. and BAKER L. W. (1977) Subclavian and axillary artery injuries. *S. Afr. Med. J* **51**, 227–231.

ROBBS J. V. and BAKER L. W. (1978a) Arterial trauma involving the lower limb. *J. Trauma.* **18**, 324–328.

ROBBS J. V. and BAKER L. W. (1978b) Major arterial trauma—review of experience with 267 injuries. *Br. J. Surg.* **64**, 532–538.

THOMPSON J. E. (1974) Acute peripheral arterial occlusion. *N. Engl. J. Med.* **290**, 950–952.

THOMPSON J. E., SIGLER L., RAUT R. S. et al. (1976) Arteria embolectomy: a 20-year experience with 163 cases. *Surgery* **67**, 212–220

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Ascaris lumbricoides and perfo[illegible] a critical review

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SUMMARY

Ileal perforation due to typhoid bacilli is the commonest cause of peritonitis in the Tropics. Perforation due to Ascaris lumbricoides is rare. Three cases of ileal perforation believed to be due to A. lumbricoides are presented and the evidence critically reviewed. It is suggested that signs of heavy infestation with A. lumbricoides make a diagnosis of intestinal perforation more likely in a patient with an acute abdomen.

A COMMON cause of peritonitis in the Tropics is distal ileal perforation. In the majority of cases this perforation is due to the activity of typhoid bacilli in the Peyer's patches concentrated in this region of the small intestine. Tuberculous ulcers, strangulated obstruction, *Strongyloides stercoralis* and trauma are also recognized aetiological agents in perforation of the small intestine. The rare, solitary, small punched-out ulcer of the small intestine may also perforate (the so-called idiopathic perforation). Crohn's disease (regional ileitis) is rare in the Tropics, and although ulceration and perforation occur in this condition among Caucasians (Gow and Walsh, 1952; Waye and Lithgow, 1967), in Africans reports are unknown.

Intestinal perforation due to the ascarid has been suspected (Evans-Amfon, 1963), and, indeed, believed by some to be a real entity (Ovnatanian, 1959; Tkebuchava, 1960; Piggott et al., 1970; McNair, 1972), but proof has been difficult to come by owing to the frequent association of ascariasis with proved cases of typhoid fever.

This author has been concerned for some time with several cases of ileal perforation with peritonitis in which no evidence, clinical, microbiological, serological or histopathological, of typhoid infection could be found, but in which *Ascaris lumbricoides* were seen lying freely in the peritoneal cavity. The following cases are typical of the diagnostic dilemma.

Case reports

Case 1: A. K., male, aged 6 years, was admitted on 25 June 1977 to the Children's Emergency Department of University College Hospital, Ibadan, with a 3-day history of abdominal distension, nausea and loss of appetite. Vomiting had not been significant, but 6 days previously six round worms had been vomited. The bowels had not opened for 6 days. There was no fever.

On examination, the child did not look ill, though he was pale and mildly dehydrated. His temperature was 37 °C and his pulse 100/min, regular and of good volume. The respiration rate was 34/min. There were no palpable lymph glands. The abdomen, which was distended uniformly, was soft and not tender. There was no muscle guarding or rebound tenderness and a percussion note was resonant. Bowel sounds were present. The rectum was empty.

The haematocrit was 33 g/dl and the leucocyte count was $6{\cdot}2 \times 10^9$/l. Biochemical tests of plasma showed Na, 118 mmol/l; K, 3·2 mmol/l; Cl, 78 mmol/l; HCO_3, 28 mmol/l. The blood urea was 7·13 mmol/l.

Abdominal radiographs demonstrated a large number of round worms and a large subdiaphragmatic gas collection. A clinical diagnosis of typhoid perforation was made and plans for operation were instituted, with correction of fluid and electrolyte loss[illegible] laparotomy, thin, watery peritoneal fluid was found, with only minimal escape of small bowel contents. A segment of ileum, approximately 25 cm long, its distal end some 150 cm from the ileocaecal valve, was the seat of multiple perforations. The perforations were rounded and punched out with surrounding induration. Within the gut lay a bolus of *A. lumbricoides*, several plugging the small bowel perforations and preventing the escape of the gut contents. There was no mesenteric adenitis and the spleen was of normal size. No other pathology was evident.

The involved segment was resected with end-to-end anastomosis. After peritoneal toilet, the wound was closed in layers with a corrugated drain placed in the pelvis and brought out through a stab wound incision. The postoperative course was complicated by *Escherichia coli* septicaemia and wound infection by the same micro-organism.

Histopathological examination of the resected specimen did not reveal the typical typhoid picture. Blood, stool, urine and peritoneal exudate cultures were negative for salmonella. The Widal agglutination reaction was negative. The Heaf test was negative. The patient was discharged on the eighteenth postoperative day.

Case 2: A. S., male, aged 8 years, was admitted with a 5-day history of central abdominal pain associated with vomiting. The mother stated that the child had 'coughed' up a round worm the previous day. The abdominal pain had become worse in the 36 h before attendance at hospital. The child had lost his appetite, had become constipated and his abdomen was enlarged. The mother thought that the boy had had a fever the previous night, but there had been no headaches. He had been well and at school in the weeks before this illness.

Examination revealed a miserable-looking boy with only moderate abdominal pain. The pulse was 94/min and regular; his blood pressure was 110/60 mmHg and his temperature was 37·8 °C. The respiration rate was 26/min. No peripheral glands were palpable. The abdomen was full and firm, but guarding was only moderate. There was tenderness in all areas. Bowel sounds were absent. The rectum contained loose faecal matter and some mucus.

The haematocrit was 38 g/dl; the white cell count was $9{\cdot}3 \times 10^9$/l, with a normal differential count. Blood urea was 7·9 mmol/l; Na, 138 mmol/l; K, 3·8 mmol/l; Cl, 91 mmol/l; HCO_3, 20 mmol/l.

Radiographs of the abdomen showed some fluid levels as well as dilated loops of small intestine.

After appropriate preparation, laparotomy was performed. Thin, bile-stained peritoneal fluid was seen. The small bowel was distended proximal to a point about 30 cm from the ileocaecal valve. In this region, loops of bowel and omentum had attempted to surround some bile-stained intestinal contents walled over by a friable pyogenic membrane. When the loops were separated, two perforations, each about 6 mm in diameter, were seen, one near the antimesenteric border of the gut, the other about midway between the mesenteric and the antimesenteric borders. They lay 10 cm apart. Two ascaris worms were found lying in the right paracolic gutter. The liver and spleen were not enlarged.

The affected loop of bowel was brought out into the wound and isolated with moist abdominal packs. The perforations were rounded, indurated and punched out. The edges of the perforation were excised and submitted for histopathological examination. The defect was closed in two layers. The wound was closed in layers, with deep tension monofilament nylon sutures *in situ*. Apart from a mild wound infection, the patient

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made an uneventful recovery. The excised specimens were reported as showing non-specific inflammatory reaction.

Cultures of peritoneal fluid, stool, blood and urine were negative for salmonella. The Widal agglutination reaction failed to show a significant rise in titre after 10 days. The Heaf test was grade 1 positive.

Case 3: R. L., male, aged 8, was admitted with a one-day history of vague abdominal pain. He had vomited several times that day as well as over the 3 days before his admission. He had had vague abdominal pains in the past, but these had settled spontaneously after a day or so. The present episode of pain was initially central, but later became generalized. One loose motion was passed immediately on arrival in hospital. No ascaris worms were known to have been passed or vomited. One week before he came to hospital he had had a fever with loss of appetite. Antimalarials had been given and had abolished the fever, whereupon he had felt better.

On examination, the child looked ill; he had dry lips and his tongue was coated. He was pale and anxious and obviously in pain. The pulse was 116/min and regular. His temperature was 38 °C. Blood urea was 5·1 mmol/l; Na, 121 mmol/l; K, 3·2 mmol/l; Cl, 88 mmol/l; HCO_3, 21 mmol/l.

The abdomen was distended and did not move with respiration. There was tenderness in the right upper and lower quadrants and guarding was mostly in this area as well as in the left iliac fossa. Bowel sounds were absent. Rectal examination was unrevealing, only some loose faecal matter being present. Plain radiographs of the abdomen were unhelpful. A diagnosis of intestinal ascariasis was made and conservative management instituted. Review 4 h later did not reveal any change but re-examination at 8 h demonstrated evidence of increasing toxicity. The pulse was now 126/min and his temperature was 38·5 °C; abdominal guarding was now more marked. Laparotomy was decided upon.

The peritoneal fluid was bile-stained and purulent. A leaf of the greater omentum was seen to be involved in an attempt to circumscribe the focus of infection. A perforation approximately 1 cm in diameter lay at a point half-way between the mesenteric and the antimesenteric borders of the gut some 100 cm from the ileocaecal valve; its edges were quite regular. A single round worm lay among the coils of small bowel while two others tried simultaneously to escape from the small bowel lumen. Another perforation, approximately 4 mm in diameter, lay about 5 cm proximal to the larger perforation. From it, too, a round worm was in the process of completely freeing itself from the bowel lumen. Just proximal to the perforations lay the main mass of *A. lumbricoides*; 37 worms were removed from this segment of ileum.

The edges of the perforation were excised and sent for histological study. Peritoneal toilet was effected and the wound closed in layers. Tetracycline was given for 7 days only. Recovery was uneventful. The specimen was reported as showing non-specific acute inflammation.

Bacteriological studies of blood, stool and peritoneal pus were positive for proteus and *E. coli*. Blood and urine cultures were negative. The Heaf test was grade 1 positive. The Widal agglutination reaction was not significant.

Discussion

Ascaris lumbricoides is a common resident of the small intestines of man in the Tropics. All age groups are affected. In some regions up to 90 per cent of the children are infested. In Ibadan, Nigeria, a study of stool specimens at the University College Hospital during a 12-month period (1976–7) found the ova of *A. lumbricoides* in 840 cases out of 2400 sampled, an incidence of 35 per cent.

Human infection is acquired by accidentally ingesting the embryonated eggs from polluted drinking water, food or infected soil. Ingested eggs reach the duodenum where their shells are softened by intestinal juices, thereby freeing the larvae. Normally, the migrating larvae hatched from eggs produce no damage. It is the mature worms which damage the wall of the small intestine by processes at present unclear. Bowel suture lines may be penetrated (McNair, 1972) and minute orifices may be entered (ducts of Santorini and Wirsung, ampulla of Vater, the appendix) to cause various pathological lesions. Penetration of the healthy intact intestinal wall may be by trauma or enzymatic digestive processes. That perforation does occur in the worm-infested bowel entirely unassisted by typhoid ulceration or other pre-existent disease is suggested by a combination of clinical and laboratory evidence.

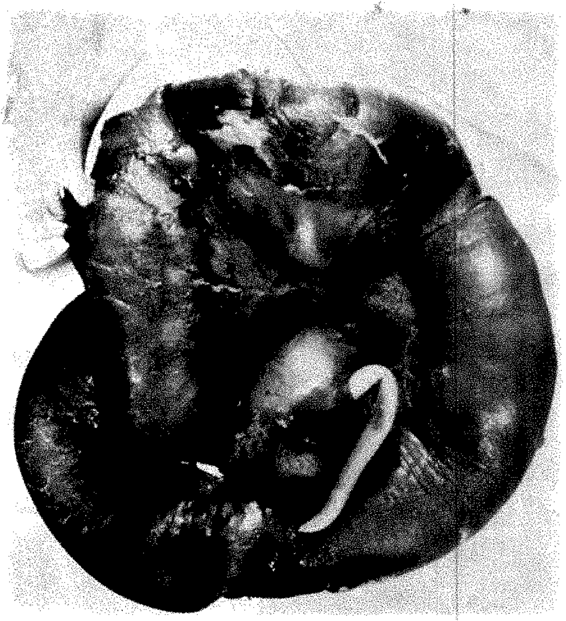

Fig. 1. *Ascaris lumbricoides* and perforation of the ileum.

Clinical

The history is short and prodromal symptoms are absent; if present they are indefinite and vague. Fever may be present in children due to the presence and activity of the worms, but the malaise, toxicity and prostration seen in typhoid fever are unusual.

Abdominal pain and vomiting are the main symptoms in uncomplicated cases. The abdominal pain is vague but may be colicky and is mainly epigastric (Swartzwelder, 1946). With perforation, the pain becomes generalized, so that the abdomen becomes full, distended and doughy. The firm, rigid abdomen and the typical facies seen in typhoid are not there. Bowel sounds may persist if spillage of ileal contents is prevented by the worms plugging the perforation and peritonitis is minimal. Vomiting occurs with obstruction by a worm bolus or the ileus secondary to peritonitis. Diarrhoea, if present, is due to spillage of ileal contents into the pelvis, although bolus obstruction by worms causes constipation, especially in children. The stool may contain worms, mucus or blood but lacks the pea-soup character of typhoid enteritis. Cachexia is rare in adult surgical cases. In children, it is associated with massive chronic infestation (Piggott et al., 1970). In such cases it is indistinguishable from the malnourished child with early typhoid perforation.

Abdominal radiographs may show the typical whirlpool pattern ('tourbillon'). With perforation subdiaphragmatic air may be seen, but this sign is indistinguishable from typhoid perforation with coexistent intestinal ascariasis.

The findings at laparotomy strengthen the case for a non-typhoid aetiology. The gut in early cases looks healthy. The perforations are usually rounded, the edges regular and not undermined. It may or may not be through a Peyer's patch and may be anywhere on the circumference of the small intestine. Typhoid perforation has a predilection for the antimesenteric border of the ileum. The lymphatic tissues, usually noted to be enlarged in typhoid fever, were not significantly enlarged in any of the cases reported. The greater omentum, that 'abdominal policeman', when fully developed, is present at the site of inflammatory reaction. In typhoid perforation this structure is conspicuously absent from the site of intestinal spillage and there is little fibrinous reaction, so that only the bowel loops are left to try to contain the spreading septic focus. Perforations may occur in any number; in the first case reported here, perforation was at six different sites.

The subsequent clinical course of the patients also supports an ascaris aetiology; the stormy postoperative course of the perforated typhoid case is unusual. The wound may be infected, as in our cases, but certainly not to the same degree as the extensive contamination and massive purulent discharge typical of typhoid perforation and which regularly initiates wound dehiscence and incisional hernia.

Laboratory data

Laboratory data assist greatly in excluding any pre-existent or concurrent disease. Microscopy and culture of peritoneal fluid, urine, blood and stool will confirm the presence of salmonella or other organisms. In the 3 cases reported above, salmonella was not isolated. The Widal agglutination reaction failed to show a significant rise in titre in any of the cases, and histopathological studies only demonstrated non-specific acute inflammatory reaction, with eosinophils in abundance at the sites of perforation. In the 2 cases sampled, the leucocyte count was within the normal range.

It is usual for at least one of the investigations to show the presence of salmonella. When the typical typhoid cellular pattern with aggregations of monocytes, basophils and lymphocytes are absent, one must search for other causes. The failure to demonstrate the presence of any of the recognized agents of ileal perforation does not necessarily implicate *A. lumbricoides* merely by their presence. Evidence of bowel wall damage by an active process of round worms is necessary to implicate them in perforation of the gut. Induration of the tissues around the perforation is a common finding, and ascaris worms are known to cause induration of the bowel wall by pressure, trauma and possibly by their toxic secretions. Advantage may also be taken of the rare, solitary, small ulcers of the small intestine. When ascaris worms are found lying freely in the peritoneal cavity and the tissue around the site of perforations is replete with eosinophil cells, the conclusion is very pressing.

It would seem from these observations that in some cases of distal ileal perforation, *A. lumbricoides* is the agent responsible. How this feat is achieved in the healthy bowel is at present conjectural; whether an enzymatic substance is secreted which dissolves the wall of the bowel or whether the worms merely take advantage of some wall weakness are two strong possibilities. Direct pressure with ulceration, necrosis and perforation would seem to be the most obvious mechanism.

It is suggested that in a patient with an acute abdomen, evidence of heavy infestation with *A. lumbricoides* makes a diagnosis of intestinal perforation more likely.

References

EVANS-AMFON E. (1963) Intestinal perforation. *Ghana Med. J.* **2**, 99–103.

GOW J. G. and WALSH A. (1952) Acute perforation in regional ileitis. *Br. J. Surg.* **39**, 445–447.

MCNAIR T. J. (ed.) *Hamilton Bailey's Emergency Surgery*, 9th ed. Bristol, Wright, p. 929.

OVNATANIAN K. T. (1959) Problem of intestinal perforation by ascariasis. *Med. Parazitol. (Mosk.)* **28**, 422–426.

PIGGOT J., HANSBARGER E. A. and NEAFIE R. C. (1970) Human ascariasis. *Am. J. Clin Pathol.* **53**, 223–234

SWARTZWELDER J. C. (1946) Clinical ascariasis: an analysis of 202 cases in New Orleans. *Am. J. Dis. Child.* **72**, 172–180.

TKEBUCHAVA C. I. (1960) Perforation of the wall of the caecum by ascaris. *Vestn. Khir.* **84**, 125–126.

WAYE J. D. and LITHGOW C. (1967) Small bowel perforation in regional enteritis. *Gastroenterology* **53**, 625–629.

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Surgical aspects of radiation injury to the intestine

R. B. GALLAND AND J. SPENCER*

SUMMARY

The clinical features are described of 37 patients requiring surgical management for radiation injury to the intestine sustained as a result of treatment of abdominal or pelvic malignancy. Twenty-nine of the patients underwent operation and only 4 remained symptom-free after the procedure. Thirteen patients died in the postoperative period, and of these, 5 were free of the original disease. Possible predisposing factors in the production of intestinal injury are discussed, as are various means of dealing with the established condition.

THE advent of radiotherapy for pelvic and abdominal malignancy has produced dramatic amelioration of many diseases, but at the cost of a wide range of gastrointestinal side effects. These may range from a mild proctitis, causing little or no problem, to a more severe injury that results in the death of the patient whilst there is an apparent 'cure' of the original disease. The incidence of these complications is difficult to assess; if one includes all gastrointestinal symptoms, it would appear to be 50–75 per cent (Maas, 1948); however, the incidence of those requiring operation ranges from 2 to 17 per cent (Aldridge, 1942; Requarth and Roberts, 1956).

This paper presents the clinical details of a series of patients who required surgical management as a result of previous radiotherapy. Malabsorption, uncomplicated enteritis, colitis and proctitis, none of which is normally managed by a surgical unit, are, therefore, not included.

Patients and methods

Thirty-seven patients, 30 women and 7 men, were included in the study. All presented for management between 1960 and 1977 inclusive. At the time of their initial radiotherapy, the age range of the women was 38–80 years (mean 54 years) and that of the men 17–67 years (mean 53·3 years).

Initial pathology

The lesions for which radiotherapy had been required are listed in *Table I*. It can be seen that the women had mainly gynaecological tumours, whereas 5 of the 7 men had cancer of the bladder.

Radiotherapy

All patients received conventional external radiotherapy, combined in the case of the cervical lesions with radium implants. During radiotherapy, 24 of the 37 patients (64 per cent) developed some form of gastrointestinal disturbance, as shown in *Table II*. As may be seen, diarrhoea was the commonest problem, occurring either alone or combined with anorexia, vomiting or abdominal pain in 21 of the 24 cases.

In the majority of these patients the condition settled on symptomatic treatment, but 4 patients required emergency operations, 3 for peritonitis and 1 for large bowel obstruction.

Timing of gastrointestinal presentation

The latent period, from the time of radiotherapy to presentation, varied greatly, small bowel lesions tending to present later than large bowel lesions, as seen in *Fig.* 1. The latent period for small bowel presentation was 0–18 years (median 2 years 11 months), whilst that for the large bowel was 0–13 years (median 1 year 4 months). This difference is significant at the 5 per cent level (Mann–Whitney U test).

Fig. 2 shows the latent period of presentation for each lesion. Perforation tended to present earliest, the range being 0–6 years (median 6·5 months). Three cases presenting with this condition did so during the course of radiotherapy. Fistula formation was seen between 8 months and 6 years 9 months (median 21 months) and haemorrhage between 3 months and 2 years 6 months (median 23 months). Stricture formation had the longest latent period, the range being 0–18 years (median 27·5 months). The difference between the times of presentation of perforation and stricture was significant at the 5 per cent level, using the Mann–Whitney U test.

Gastrointestinal injuries sustained

The manner of presentation varied with the type of lesion subsequently identified, the latter being shown in *Table III*. Of the 37 patients studied, 23 patients had only one lesion and 14 had multiple lesions. Multiple lesions were noted at the original presentation in 8 patients, and a further 6 patients developed second or third lesions after an interval.

A total of 54 separate lesions was noted, with almost equal numbers occurring in the large and small bowel. The commonest lesion seen was that of stricture formation, there being almost equal numbers of fistulas, perforations and cases of gastrointestinal bleeding. Of the small bowel fistulas, those of the mid-ileum were to the colon and the vagina respectively; those of the terminal ileum were to the bladder and to a chronic abscess cavity. The large bowel fistulas were to the bladder (3) and ileum from the sigmoid colon, and to the vagina (2) and the uterus from the rectum.

Diagnosis

The diagnosis of the lesions was, in most cases based on clinical grounds, though often confirmed radiologically. Biopsy, particularly in the case of the rectal and some of the sigmoid lesions, was also helpful. All tissue removed was sent for histological examination and was diagnosed as having features characteristic of radiation damage.

Table I: ORIGINAL DISEASE REQUIRING RADIOTHERAPY

Women	
Carcinoma of cervix	14
Carcinoma of endometrium	9
Carcinoma of ovary	4
Hypernephroma	2
Carcinoma of bladder	1
Men	
Carcinoma of bladder	5
Hypernephroma	1
Teratoma of testis	1

Table II: SYMPTOMS APPEARING DURING RADIOTHERAPY

Diarrhoea	
Alone	7
With pain	6
With anorexia/vomiting	6
With pain, anorexia/vomiting	2
Without diarrhoea	
Anorexia/vomiting	2
Anorexia/vomiting, pain	1
Total	24

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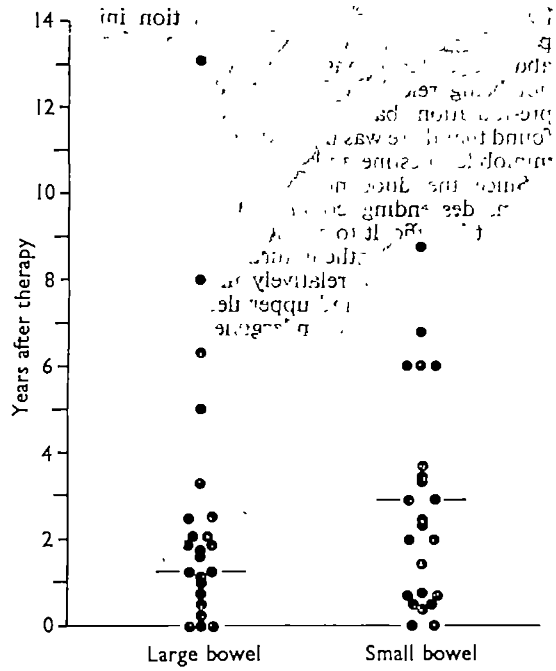

Fig. 1. Time of presentation of large and small bowel lesions after radiotherapy. (Bars represent medians.)

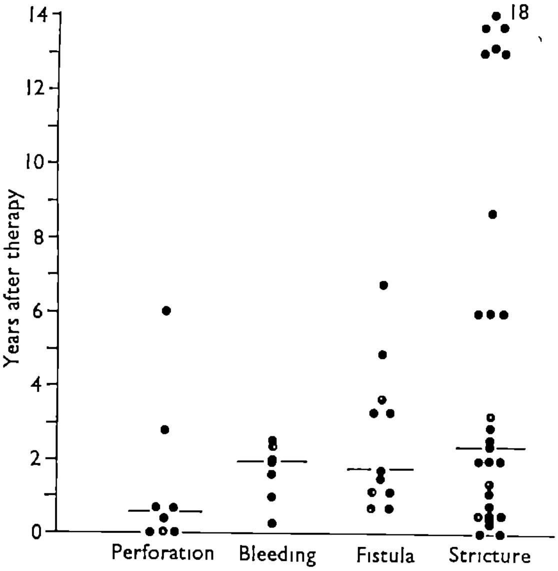

Fig. 2. Time of presentation of the various lesions encountered after radiotherapy. (Bars represent medians.)

Management

Management of these patients was conservative whenever possible in all except the 4 patients requiring urgent operative treatment during their course of radiotherapy. All but 8 patients, however, eventually came to operation. Of those 8 patients, 3 had ileal strictures diagnosed on barium follow-through examination, 3 had bleeding rectal ulcers that eventually healed and 2 had vesicocolic fistulas and died of renal failure before an operation could be performed.

Table IV shows the operations performed for the upper gastrointestinal lesions. The course in those who underwent

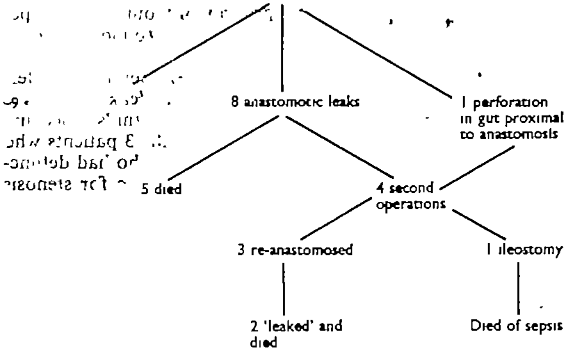

Fig. 3. Course of 18 patients who underwent small bowel resection with primary anastomosis.

Table III: INTESTINAL LESIONS ENCOUNTERED

	Stricture	Fistula	Perforation	Haemorrhage	Total
Duodenum	1			1	2
Jejunum	2		1		3
Mid-ileum	5	2	3		10
Terminal ileum	11	2			13
Transverse colon			1		1
Sigmoid colon	5	4	3		12
Rectum	4	3		6	13
Total	28	11	8	7	54

Table IV: OPERATIONS FOR SMALL BOWEL LESIONS

Gastrectomy		1
Resection with anastomosis		
Jejunum	2	18
Mid-ileum	6	
Terminal ileum	10	
Bypass		2
Suture of perforation		1
Total		22

Table V: OPERATIONS FOR LARGE BOWEL LESIONS

Defunctioning colostomy		10
Resection with anastomosis		
With colostomy	4	5
Without colostomy	1	
Hartmann's procedure		1
Suture of perforation		1
Total		17

Table VI: POSSIBLY RELEVANT PAST HISTORY

Previous abdominal operation	
Operation associated with presenting condition only	13
Operation for unassociated condition	6
Operation for both presenting and unassociated conditions	3
Cardiovascular disease	
Hypertension	4
Aortic aneurysm	1
Intermittent claudication	1
Previous pelvic sepsis	3

[illegible] small bowel a[illegible] noted that the mortality in this group was 8[illegible] cent) and that 3 of the patients who died were [illegible] to be free of tumour.

Similarly, *Table V* shows the large bowel op[illegible] taken. Two of the 5 primary anastomoses [illegible] th[illegible] patelnts died; a further patient having a Hartma[illegible] re[illegible] also died postoperatively of sepsis. Two of the [illegible] died were free of tumour. Of the 10 patients wh[illegible] tioning loop colostomies, 4 required reoperation [illegible] at the stoma.

Thus, of the 29 patients requiring surgery, 13 (45 per cent) subsequently died, of whom 5 were free of the original disease. Of those patients surviving surgery, only 4 remained totally free of gastrointestinal symptoms on subsequent follow-up.

Past medical history

All but 10 patients had factors in their past medical histories which may be relevant. *Table VI* shows that the commonest factor was a previous operation. Six patients had suffered some form of cardiovascular disease and 3 had had previous pelvic sepsis. In several patients more than one factor was in evidence.

Finally, 7 of the 37 patients had severe radiation cystitis, 1 requiring cystectomy, while 1 patient had a radiation myelopathy and 1 had malabsorption.

Discussion

The effect of ionizing radiation on the gastrointestinal tract is twofold. First, there is a direct effect on the gut wall itself (Quastler, 1956), occurring during or shortly after the course of radiotherapy, and secondly, there is a progressive obliterative vasculitis (Warren and Friedman, 1942) which may produce ischaemic intestinal problems many years after treatment.

In our series, the earlier presentation of perforation compared with stricture ($P < 0.05$) suggests that the former is due mainly to the direct effect on the gut wall, ischaemia being relatively more important in the case of stricture formation. Haemorrhage and fistula formation appear to occupy an intermediate position.

One would expect the vasculitis effect to be enhanced by arterial insufficiency due to any other cause. De Cosse et al. (1969), when comparing 100 patients suffering from radiation injury with 227 consecutive uninjured treated patients, found that hypertension, diabetes and cardiovascular disease were all significantly more common in the injured group. In our series 6 patients were regarded as having significant cardiovascular disease, 4 of these being hypertensive; no patient had diabetes mellitus.

Other factors that have been regarded as important in inducing radiation injury are excessive radiation dosage and previous operation or sepsis.

Excessive radiation has been mentioned as a possible causative factor in the production of intestinal injury. Jackson (1976) stated that 21 per cent of 52 patients in his series were subjected to high or very high doses. Only 3 of the 37 patients were regarded as having excessive radiation, however, and in each case, this was due to further courses of treatment undertaken in an attempt to eradicate recurrence of the original tumour.

The role of previous abdominal operation or sepsis and the subsequent adhesion formation is uncertain; theoretically at least, adhesions, by immobilizing the intestine, may increase the likelihood of any one section of bowel receiving too high a dose of radiation (Localio et al., 1969; Maruyana et al., 1974). De Cosse et al. (1969), however, found that only previous hyste[illegible] predisposed to radia[illegible]jury when [illegible]elvic [illegible]therapy [illegible] being considered, other [illegible]dominal operations and previous sepsis apparently [illegible]levant. Green et al. (1975), performing [illegible] barium followthrough examinations, [illegible] relationship between relatively [illegible] previous operations.

[illegible] terminal ileum, ascending colon [illegible] and rectum are relatively fixed, it is difficu[illegible]ow formation of adhesions could immobilize [illegible]ther. However, adhesion formation may be [illegible] more important in the jejunum and mid- and [illegible]um. In our series, 22 of the 37 patients had undergone previous operations, 16 of these patients requiring operation for the presenting malignant disease. All of the 11 patients in whom 14 lesions of the jejunum, mid-ileum or transverse colon subsequently developed had undergone previous operation.

The diagnosis of radiation injury should always be considered in patients who have had previous radiotherapy and who present with abdominal symptoms. The latent period was as long as 18 years in 1 patient in this series and it is clearly important not to misdiagnose patients presenting with abdominal problems as having secondary malignancy.

A review of the surgical management of radiation injury to the small intestine has recently been published (Swan et al., 1976). Twenty-eight series produced 199 patients and a further 45 patients were added by the authors themselves. In the original 199 patients, the mortality was 21 per cent for those having a resection with primary anastomosis and 10 per cent for those having the lesion bypassed, the anastomotic leakage rate being 36 per cent and 6 per cent respectively. Similarly, in their own series of 45 patients, there was a mortality of 53 per cent and 7 per cent for the resection and bypass groups respectively, anastomotic leakage rates being 65 per cent and 11 per cent.

In our series, 8 of 18 patients having a resection and primary anastomosis of the small bowel developed an anastomotic leak and 1 patient developed a perforation proximal to an intact anastomosis. Of these 9 patients, only 1 survived. Of the 2 patients having a bypass, neither anastomosis leaked and both patients survived. These figures suggest that even though bypass surgery may theoretically result in a subsequent 'stagnant loop' syndrome, it may be preferable to resection with a primary anastomosis. Should resection and anastomosis be undertaken, wide resection is advisable since the extent of the bowel damage is often much greater than expected (Wellwood et al., 1974).

In our series, 1 patient developed peritonitis caused by a perforation 12 cm proximal to an intact anastomosis, the bowel being diseased histologically although macroscopically normal at the original laparotomy.

A temporary loop jejunostomy or ileostomy may be used to cover the anastomosis (Jackson, 1976).

Similarly, in colonic lesions, simple procedures fared better than more radical operations. None of the 10 patients who had defunctioning colostomies died, in contrast to 2 out of 5 patients who died after resection and primary anastomosis.

With the generally unsatisfactory results of surgical management of patients with radiation injury to the gut, avoidance of the problem is clearly the ideal. At-risk groups appear to be identifying themselves, these being those patients having had previous pelvic operations or sepsis, those having cardiovascular problems or diabetes mellitus and also the group of thin, elderly, female patients shown by Green et al. (1975) to have a deep pelvis, containing a greater amount of small intestine than usual. Modification of the usual radiotherapy technique may be needed for all these patients, who also require careful long term follow-up.

References

ALDRIDGE A. H. (1942) Intestinal injuries resulting from irradiation treatment of uterine carcinoma. *Am. J. Obstet. Gynecol.* **44**, 833–854.

DE COSSE J. J., RHODES R. S., WENTZ W. B. et al. (1969) The natural history and management of radiation-induced injury of the gastrointestinal tract. *Ann. Surg.* **150**, 369–384.

GREEN N., IBA G. and SMITH W. R. (1975) Measures to minimise small intestine injury in the irradiated pelvis. *Cancer* **35**, 1633–1640.

JACKSON B. T. (1976) Bowel damage from radiation. *Proc. R. Soc. Med.* **69**, 683–686.

LOCALIO A., STONE A. and FRIEDMAN N. (1969) Surgical aspects of radiation enteritis. *Surg. Gynecol. Obstet.* **129**, 1163–1172.

MAAS J. M. (1948) Intestinal changes secondary to irradiation of pelvic malignancies. *Am. J. Obstet. Gynecol.* **56**, 249–259.

MARUYAMA Y., VAN NAGELL J. R., UTLEY J. et al. (1974) Radiation and small bowel complications in cervical carcinoma therapy. *Radiology* **112**, 699–703.

QUASTLER H. (1956) The nature of intestinal radiation death. *Radiat. Res.* **4**, 303–320.

REQUARTH W. and ROBERTS S. (1956) Intestinal injuries following irradiation of pelvic viscera for malignancy. *Arch. Surg.* **73**, 682–688.

SWAN R. W., FOWLER W. C. and BORONOW R. C. (1976) Surgical management of radiation injury to the small intestine. *Surg. Gynecol. Obstet.* **142**, 325–327.

WARREN S. and FRIEDMAN N. B. (1942) Pathology and pathologic diagnosis of radiation lesions of the gastrointestinal tract. *Am. J. Pathol.* **18**, 499–501.

WELLWOOD J. M., JACKSON B. T. and BATES T. D. (1974) Breakdown of small bowel anastomosis after pelvic radiotherapy. *Ann. R. Coll. Surg. Engl.* **54**, 2–4.

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Thyroid cancer in Kuwait: review of 117 cases*

K. A. EL-GHAMRAWI AND M. S. KHALIFA†

SUMMARY

One hundred and seventeen patients with thyroid cancer were seen at the Radiotherapy and Isotope Centre, Al-Sabah Hospital, Kuwait, between 1963 and 1974. Thyroid cancer constituted 4·7 per cent of all cancer cases among females and 2·4 per cent among males. Of these carcinomas, 58 per cent were papillary, 25 per cent follicular, 11 per cent anaplastic and 1·7 per cent medullary. Four cases (3·4 per cent) were of malignant lymphoma. The 10-year survival was 74, 96 and 21 per cent for papillary, follicular and anaplastic tumours respectively. The present series confirms the prognostic value of age, sex and histology and shows that node metastasis does not prejudice survival. The study does not show any correlation between the type of operation and survival.

THYROID cancer differs from many other neoplasms in that incidence and type differ widely in various geographical areas (Waterhouse et al., 1976). It is noted that among females in Kuwait, carcinoma of the thyroid is the second commonest type of cancer (Omar and El-Ghamrawi, 1976) and represents the commonest form of head and neck tumour (Parikh and El-Ghamrawi, 1977).

This relatively high frequency has stimulated this review of the cases managed since 1963. This series represents all cases of thyroid cancer diagnosed in Kuwait during this period, as there is a general agreement with surgeons to refer all cases to us for postoperative treatment. Some cases may have been missed during the earlier period of the study, before the establishment of the Cancer Registry in 1971.

Patients

During the period of the study we had on our records 117 cases of thyroid cancer, of which 69 were females and 48 were males, a sex ratio of 1·4 : 1. These cases represented 4·7 per cent of all female cancer patients and 2·4 per cent of all male cancer patients.

The mean age for females was 42 years±14·0 standard deviation, and for males, 49±20. No difference was observed in the mean age between Kuwaitis and non-Kuwaitis. The age-corrected incidence for different age groups is shown in *Figs.* 1 and 2 for females and males respectively.

All patients except 6 had histopathological confirmation of the presence of tumour and were subdivided according to the World Health Organization classification (Hedinger and Sabin, 1974). These 6 patients were elderly, refused surgery and the diagnosis was clinically certain. Needle biopsy was not then our common practice.

Results

Papillary carcinoma was the commonest (58 per cent) of the tumours, followed by follicular (20 per cent) and anaplastic (11 per cent) (*Table I*). Papillary and follicular carcinomas were more frequent during the third and fourth decades of life. Anaplastic tumours were commonest during the seventh and eighth decades.

The common clinical presentations are shown in *Table II*. Goitre was the commonest presentation (81 per cent).

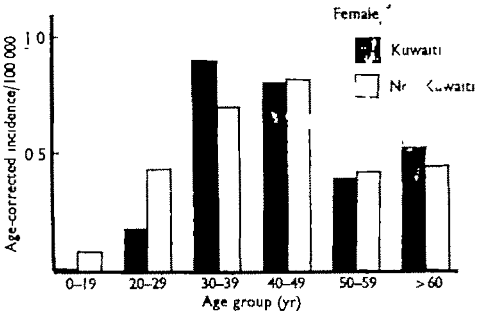

Fig. 1. Age corrected incidence for females.

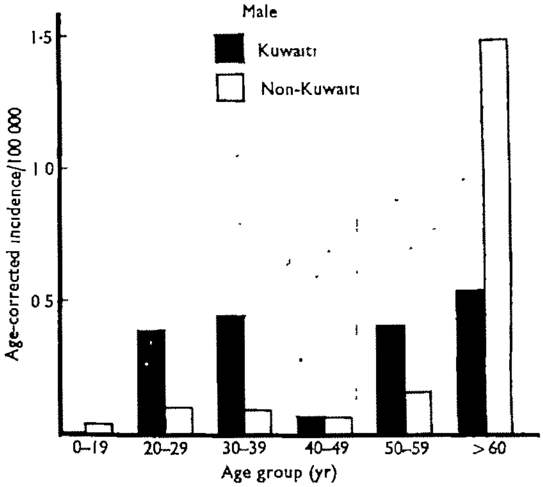

Fig. 2. Age-corrected incidence for males.

All cases with confirmed histology were retrospectively staged according to the TNM system recommended by the International Union Against Cancer (UICC, 1974). The relation of clinical staging to histology is shown in *Table III*. Over 50 per cent of patients presented at early stages T1–2 N0.

Towards the end of this study there was a trend towards more radical surgery (total and subtotal thyroidectomy), but neither histology nor the stage of the primary tumour seemed to influence the type of operation performed.

Thirty-eight patients (32·5 per cent) had palpable cervical nodes. Ten had block dissection, 15 total excision of palpable nodes, 5 excision biopsy and 6 no surgery to palpable nodes.

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Table I: DIST HISTOLOGY

Histological type					
Papillary					
Follicular					
Anaplastic					
Medullary					
Lymphoma (malignant)	4	3·4	2	2	1·0
No histology	6	5·1	3	3	1·0
Total	117	100	69	48	

Table II: COMMON CLINICAL PRESENTATIONS

	No.	%
Non-toxic goitre	95	81·2
Toxic goitre	3	2 6
Cervical nodes	12	10 3
Distant metastases	7	5·9

Table III: DISTRIBUTION OF CASES ACCORDING TO TNM STAGE AND HISTOLOGY

TNM		P	F	A	L	Total No.	%
T1–2	N0	24	16	4	1	57	51·4
	N1	21	2	2	1	26	23 4
	N2	—	—	1	—	1	0·9
	N3	2	1	1	—	4	3·6
T3	N0	4	4	—	1	9	8·1
	N1	2	—	1	—	3	2·7
	N2	—	—	—	1	1	0 9
	N3	1	—	2	—	3	2·7
M1		4	1	2	—	7	6·3

P, Papillary; F, follicular; A, anaplastic, L, lymphoma.

Table IV: CAUSES OF DEATH

	No.	%
Primary disease	22	76
Respiratory obstruction	3	10
Immediate postoperative death	3	10
Cardiovascular complications	1	4
Total	29	100

Table V: HISTOLOGY OF THE FATAL CASES

	No. fatal	Total cases	% fatal
Papillary	14	68	20 6
Follicular	1	24	4·2
Anaplastic	10	13	76·9
Lymphoma	1	4	25·0
No histology	3	6	50·0
Total	29	115	25·2

Postoperative adjuvant irradiation was given on 70 occasions (10 patients received deep X-ray and 60 had cobalt teletherapy). Sixty-three patients received therapeutic doses of radioactive iodine with or without external irradiation. Two cases with advanced metastatic disease received chemotherapy (Velbe and Endoxan). All the patients were kept on either replacement hormonal therapy (Eltroxin 150 µg daily) for undifferentiated tumours or high suppressive doses (Eltroxin 300 µg daily) for differentiated tumours.

Survival was calculated from the date of definitive treatment to 31 December 1976. Survival curves were computed using the actuarial method (Berkson and Gage, 1950). Difference in survival between the various groups was tested using the χ^2 test at a confidence level of 0·05. We analysed our results according to various factors known to influence prognosis: these are age, sex, histology, cervical adenopathy and type of surgery. Ten-year survival was 71 per cent: females did significantly better than males—74 per cent survival versus 64 per cent. Younger patients had a significantly better prognosis, probably because of the influence of histology. Follicular and papillary tumours were associated with a significantly better prognosis than anaplastic tumours (*Fig.* 3). Neither the presence of positive nodes nor the type of surgery was found to influence prognosis significantly. This could be explained by the fact that the majority of our patients received postoperative irradiation, which may have improved the expected poorer results following conservative surgery and in those with metastatic nodes.

Twenty-nine patients were known to have died during the period of the study. The commonest cause of death was the primary disease, which accounted for 76 per cent of the deaths (*Table IV*). Anaplastic carcinoma was the most fatal histological type (*Table V*).

5) The aetiology and diagnosis of malignant thyroid gland. *Br. J. Surg.* 62, 760–764.

A. H. (1974) *Cancer Handbook of Epidemiology* *sis*. Edinburgh, Churchill Livingstone, p. 174.

MUIR C., CORREA P. et al. (1976) *Cancer Incidence ntinents*, Vol. III. Lyon, International Agency arch on Cancer.

D., DONIACH I., BJARNASON O. et al. (1977) Thyroid cer in an iodide rich area. A histopathological study. *r* 39, 215–222.

W. (1954) Cancer of the thyroid and radiotherapy. *ol.* 27, 537–552.

VOLL R. V. (1961) Childhood thyroid 734–743.

K B. M. et al. (1961) Classi-inoma. A study of *J. Surg.* 102,

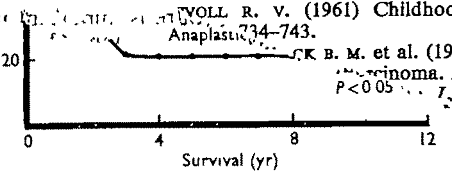

Fig. 3. Ten-year survival according to histology.

Discussion

Kuwait has a peculiar population composition: 47 per cent are Kuwaiti, 42 per cent are non-Kuwaiti Arabs and only 11 per cent are non-Arabs. Fifty-seven per cent are male and 43 per cent female. Eighty-six per cent are below the age of 40. In Kuwait the incidence of thyroid cancer is 2·8 females and 1·9 males per 100 000 of the population. This is a higher incidence than the 1 per cent reported from non-endemic parts of the world (Waterhouse, 1974; Staunton and Greening, 1976). There is no significant difference in the age-corrected incidence of thyroid cancer among Kuwaiti and non-Kuwaiti females (*Fig.* 1), whereas thyroid cancer is more common among Kuwaiti males below the age of 60 and more common among non-Kuwaiti males above 60 years of age (*Fig.* 2).

The aetiology of thyroid cancer is not always clear, but certain factors associated with a high frequency of thyroid tumours have been described, such as accidental irradiation during childhood (Duffy and Fitzgerald, 1950; Winship and Rosvoll, 1961; Modan et al., 1974; Wade, 1975), a prolonged high level of thyroid-stimulating hormone (TSH) (Purves and [illegible] ...cer is common. Criteria [illegible] benign from malignant non- [illegible] have been defined (Hurxthal and Heine- [illegible] 958; Suakal, 1959). The incidence of cancer in apparently benign goitre varies between 9 and 66 per cent (Hurxthal and Heinemann, 1958; Till, 1965; Campbell and Sage, 1975). The corresponding figures for solitary nodules vary between 2·7 per cent (Campbell and Sage, 1975) and 33 per cent (Cattell and Colcock, 1953). In the present retrospective survey attempts to estimate the incidence of solitary nodules from the patients' files were difficult and inaccurate. It is known that only 50 per cent of clinically solitary nodules are truly solitary (Taylor, 1969).

Any discussion of the results of treatment of thyroid cancer must take into consideration the prognostically significant characteristics of any series, such as age, sex and histology (Sloan, 1954; Halnan, 1966, 1975) and the long natural history of many tumours. Therefore, every series is unique. Evaluation of treatment must consider also the extent of thyroid resection, treatment of metastatic nodes and the value of postoperative external irradiation and of radioactive iodine. In papillary carcinoma, total thyroidectomy is favoured by many surgeons (Hirabayashi and Lindsay, 1961; Clark et al., 1966) because 80 per cent of papillary tumours are multifocal and spread in both lobes (Russel et al., 1963). Owing to the high morbidity of total thyroidectomy, however, subtotal thyroidectomy is becoming more popular (Staunton and Greening, 1976; Woolner et al., 1976) except where a gross lesion indicates total thyroidectomy. In follicular carcinoma total thyroidectomy has been recommended (Staunton and Greening, 1976) because of the poor results of less radical surgery. Our study, on the contrary, showed good results for follicular carcinoma (*Fig.* 3). Undifferentiated (anaplastic) carcinoma raises different problems. The majority of tumours present when advanced and radical surgery is impossible. Most authors advocate complete tumour removal and subsequent external irradiation.

The problem of metastatic nodes is of particular importance in papillary tumours. Crile (1957) advocated individual removal of metastatic nodes. Most recent studies have shown that radical dissection gives better results than conservative node surgery (Woolner et al., 1961; Franssila, 1971; Lindahl, 1975; Staunton and Greening, 1976). In our series neither the type of surgery nor the presence of node metastases influenced prognosis significantly. This may be due to the aggressive postoperative radiotherapy given to the majority of patients. However, assessment of the value of adjuvant irradiation presents difficulties as it often forms one part of a combined plan of treatment. Most advanced inoperable cases are treated by radiotherapy and there is no controlled clinical trial comparing the

[illegible] ation [illegible] Haln [illegible] y ca [illegible] e i [illegible] nt [illegible] who [illegible] t receive adju[illegible] in pa[illegible] who had postop[illegible] pract[illegible]. The value of postop[illegible] anaplastic tumours is universall[illegible] are still poor. The value of radica[illegible] metastatic disease and for differentiated [illegible] combination with surgery, has be[illegible] repeate[illegible] (Smithers, 1951; Halnan, 1969; Pochin, 1971; [illegible] 1975).

In our present practice we depend more o[illegible] sive radioiodine therapy, together with suppre[illegible] high doses of Eltroxin adjusted by repeated T[illegible] estimation, in the initial treatment of papillary a[illegible] follicular carcinoma and on multiple chemotherap[illegible] with supervoltage for anaplastic tumours.

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References

AXELRAD A. A. and LEBLOND C. P. (1955) Induction of thyroid tumours in rats by low iodine diet. *Cancer* **8**, 339–367.

BERKSON J. and GAGE R. P. (1950) Calculation of survival rates for cancer. *Proc. Mayo Clinic* **25**, 270.

CAMPBELL D. J. and SAGE R. H. (1975) Thyroid cancer: twenty years' experience in a general hospital. *Br. J. Surg.* **62**, 207–214.

CATTELL R. B. and COLCOCK B. P. (1953) The present day problem of cancer of the thyroid. *J. Clin. Endrocrinol. Metab.* **13**, 1408–1415.

CLARK R. L., IBANEZ M. L. and WHITE E. C. (1966) What constitutes an adequate operation for carcinoma of the thyroid? *Arch. Surg.* **92**, 23–26.

CRILE G. jun. (1957) The fallacy of conventional radical neck dissection for papillary carcinoma of the thyroid. *Ann. Surg.* **145**, 317–320.

DONIACH I. and WILLIAMS E. D. (1962) The development of thyroid and pituitary tumours in the rat 2 years after partial thyroidectomy. *Br. J. Cancer* **16**, 222–231.

DUFFY B. J. and FITZGERALD P. J. (1950) Thyroid cancer in childhood and adolescence. *Cancer* **3**, 1018–1032.

FRANSSILA K. (1971) Value of histologic classification of thyroid cancer. *Acta Pathol. Microbiol. Scand.* **225**, Suppl. 225, pp. 1–76.

HALNAN K. E. (1966) The influence of age and sex on incidence and prognosis of thyroid cancer. *Cancer* **19**, 1534–1536.

HALNAN K. E. (1969) *Thyroid Cancer.* Berlin, Springer-Verlag, p. 332. (UICC Monograph Vol. 12.)

HALNAN K. E. (1975) The non-surgical treatment of thyroid cancers. *Br. J. Surg.* **62**, 769–771.

HEDINGER C. H. and SABIN L. (1974) World Health Organization of Thyroid Tumours. Geneva, WHO.

HIRABAYASHI R. N. and LINDSAY S. (1961) Carcinoma of the thyroid gland: a statistical study of 390 patients. *J. Clin. Endocrinol Metab.* **21**, 1596–1610.

HURXTHAL L. M. and HEINEMANN A. C. (1958) Nodular goitre and thyroid cancer. *N. Engl. J. Med.* **258**, 457–465.

LINDAHL F. (1975) Papillary thyroid carcinoma in Denmark 1943–1968. *Cancer* **36**, 540–552.

MODAN B., BAIDATZ D., MART H. et al. (1974) Radiation-induced head and neck tumour. *Lancet* **1**, 277–279.

OMAR Y. T. and EL-GHAMRAWI K. A. (1976) Carcinoma of the cervix in Kuwait. *J. Kuwait Med. Assoc.* **10**, 141–148.

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nce of Otolary the

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(1971) In: WER

roid. New York,

and GRIESBACH W.

thyroid tumours treated

xp. Pathol. 28, 46–53.

IBANEZ M., CLARK R. L. et al. Thyroid

classification, intraglandular dissemination and athological study based upon whole organ sections ands. Cancer 16, 1425–1460.

(1954) Of the origin and characteristics and our of thyroid cancer. J. Clin. Endocrinol. Metab. 14, 335.

W. (1951) Some varied applications of radioactive es to the localisation and treatment of tumours. Radiol. (Stockh.) 35, 49–61.

ON M. D. and GREENING W. P. (1976) Treatment of thyroid cancer in 293 patients. Br. J. Surg. 63, 253–258.

KAL L. B. (1959) The problem of malignancy in nodular goitre. JAMA 170, 405–412.

TAYLOR S. (1969) The solitary thyroid nodule. J. R. Coll. Surg. Edinb. 14, 267–270.

TILL A. S. (1965) Types of carcinoma of the thyroid and their presentation. Br. J. Surg. 52, 734–735.

TOLLEFSEN H. R., SHAH J. P. and HUVOS A. G. (1972) Papillary cancer of the thyroid. Am. J. Surg. 124, 468–472.

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fication and prognosis of thyroid ca 885 cases observed in a 30-year period. Am. 354–387.

WOOLNER L. B., BEAHRS O. H., BLACK B. M. et al. (1966) Thyroid carcinoma: general considerations and follow-up data on 1181 cases. In YOUNG S. and INMAN D. R. (ed.) Thyroid Neoplasia. New York, Academic Press, pp. 51–76.

WOOLNER L. B., MCCONAHEY W. M., BEAHRS O. M. et al. (1976) Primary malignant lymphoma of the thyroid. Review of 46 cases. Am. J. Surg. 111, 502–523.

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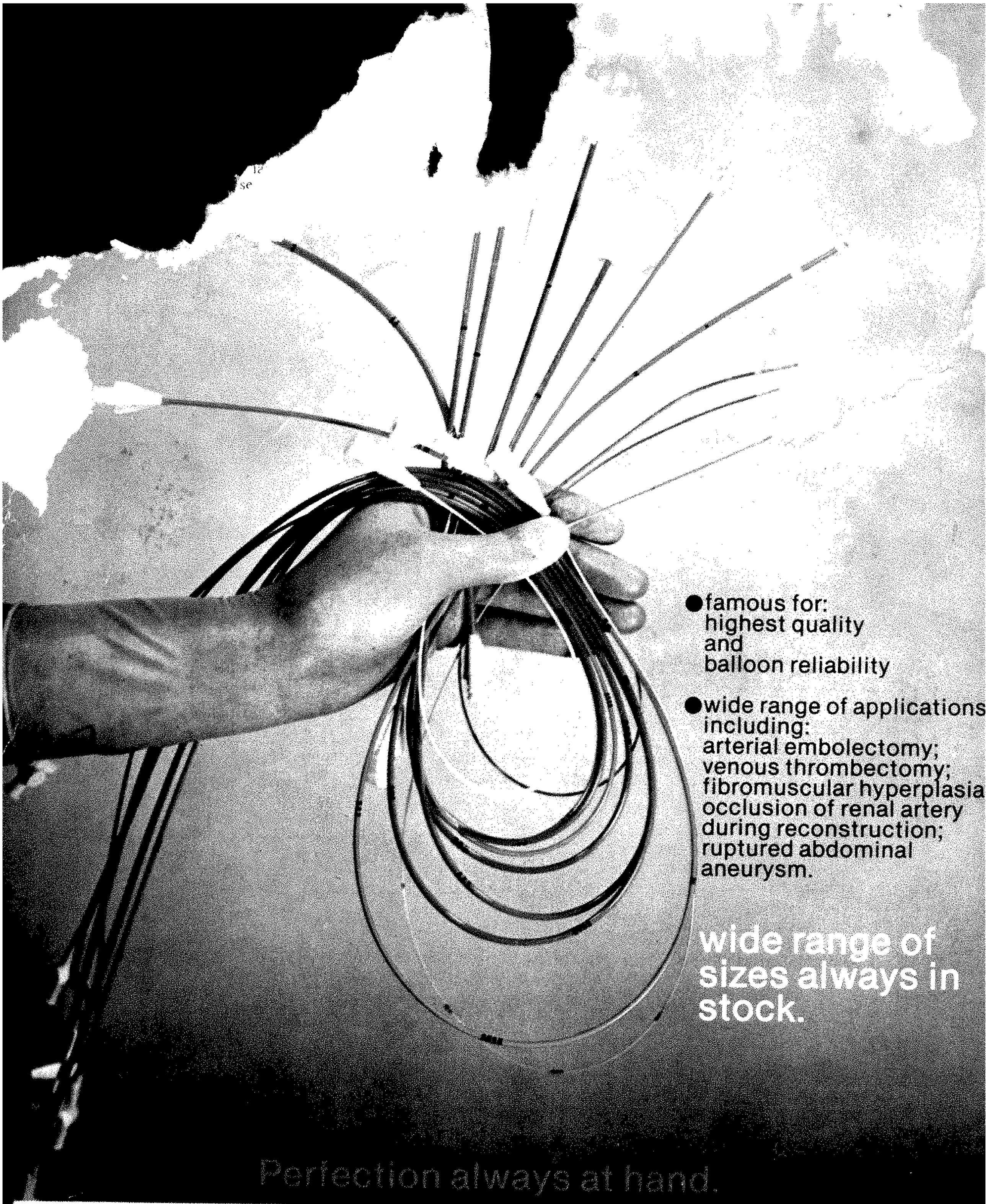

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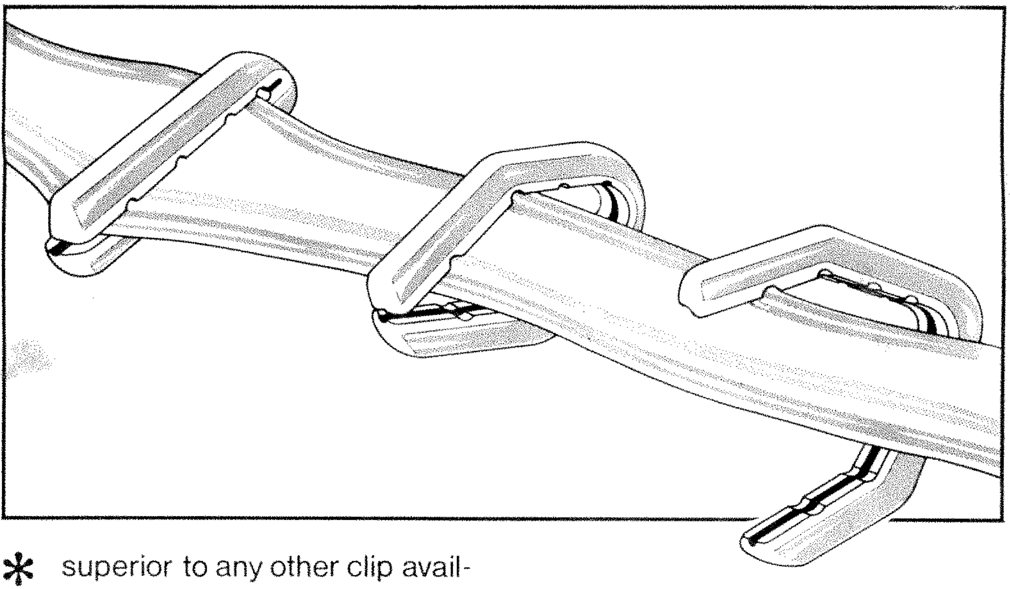

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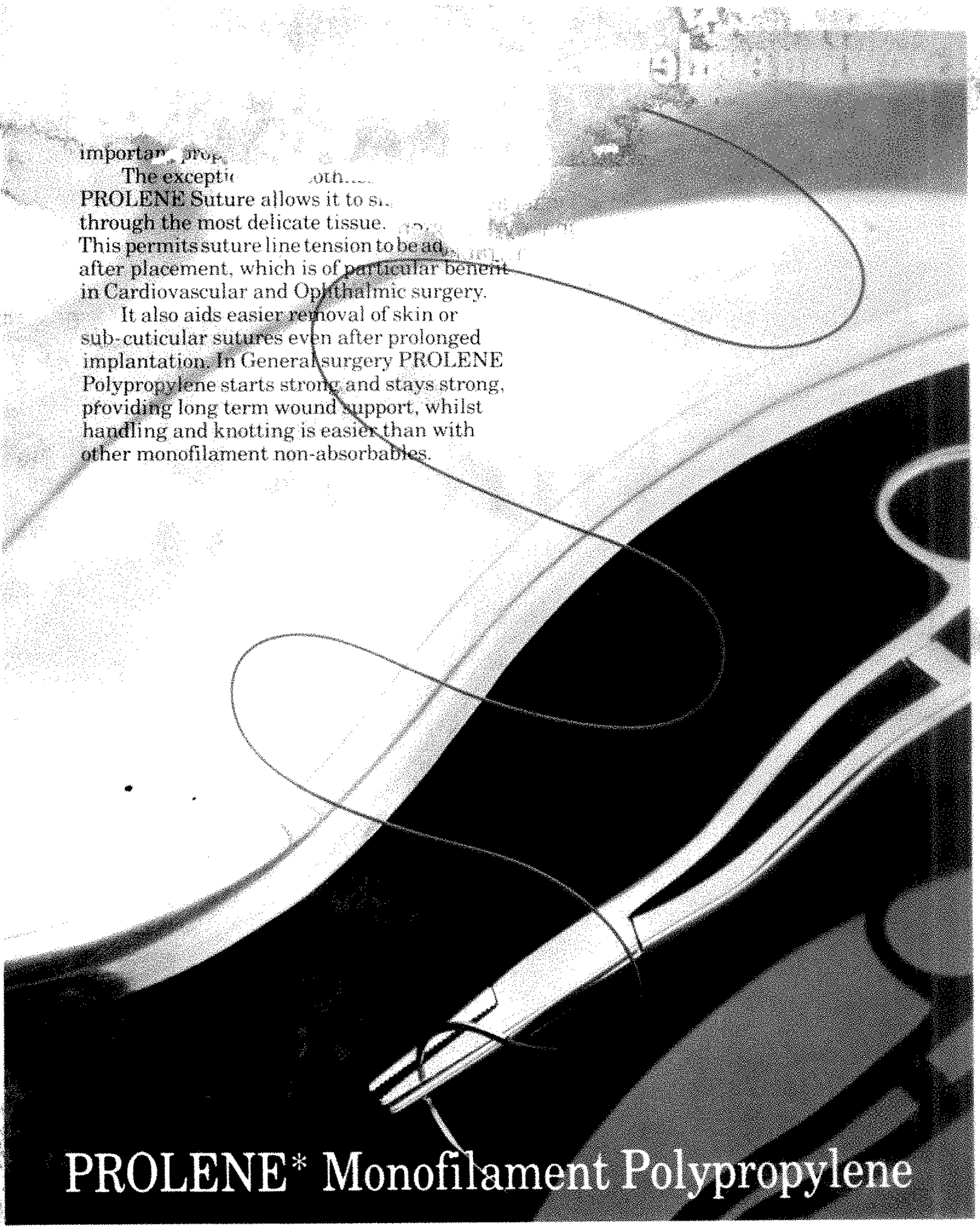

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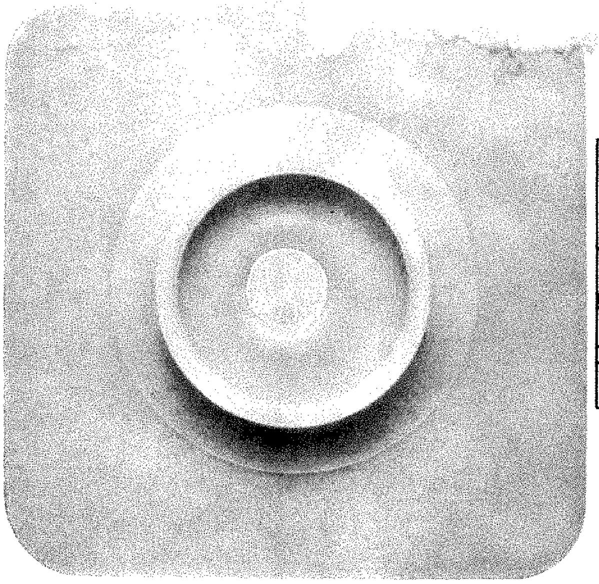

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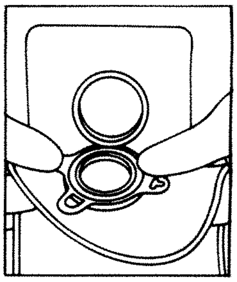

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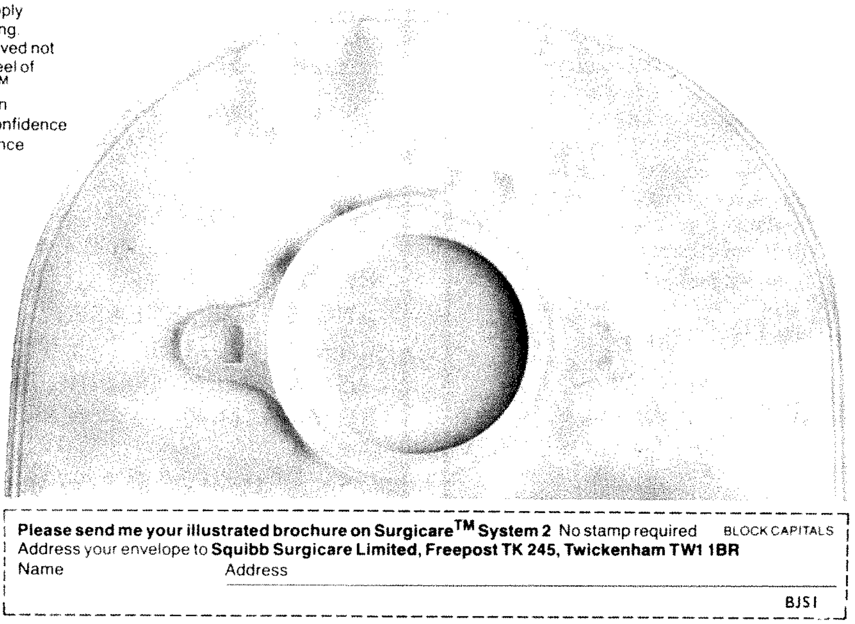

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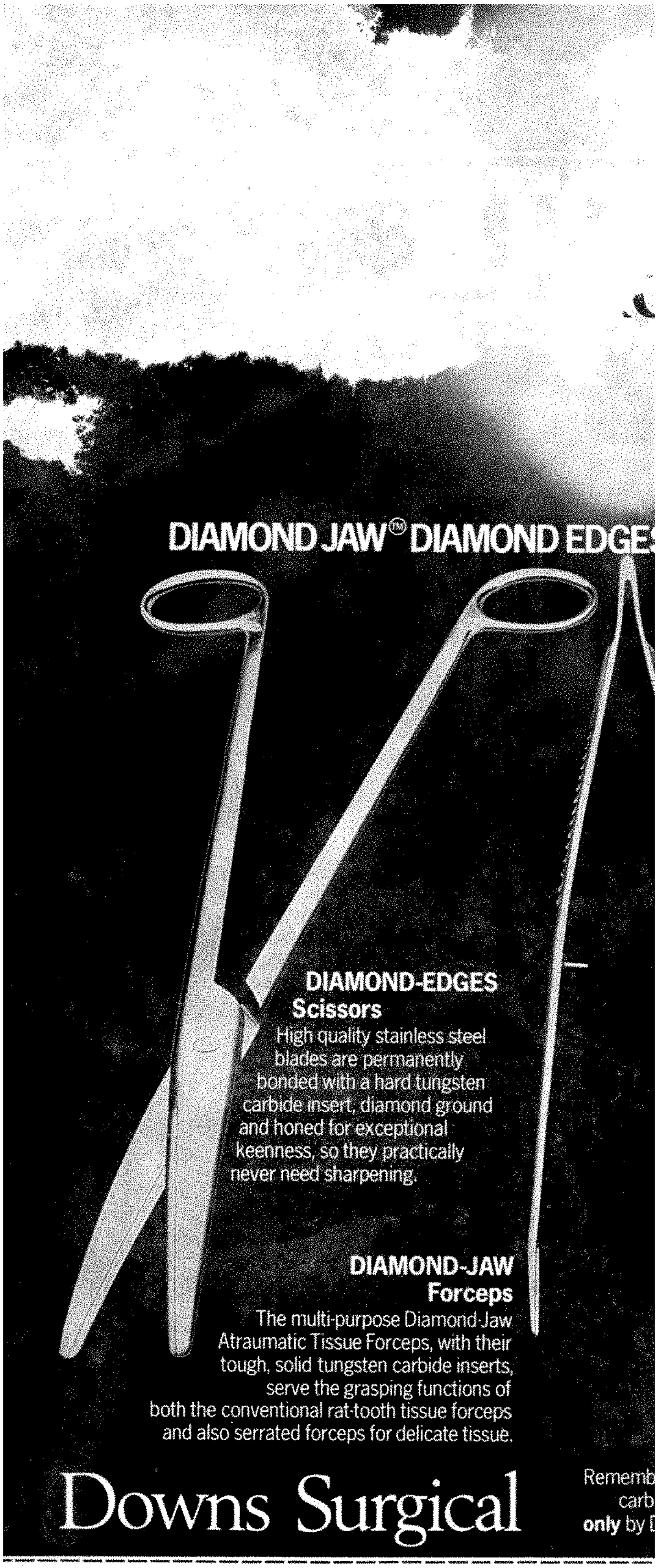

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A prospective randomized trial of vagotomy in chronic duodenal ulceration

C. G. KOFFMAN, J. B. ELDER, I. E. GILLESPIE, P. C. GANGULI, D. G. OSTICK, D. J. COWLEY, I. W. DYMOCK, D. E. F. TWEEDLE, P. F. SCHOFIELD, C. D. R. PENGELLY, M. SHAFIQ, D. R. SHREEVE AND M. PALMER

SUMMARY

In a prospective, randomized trial, 76 patients with duodenal ulceration treated by truncal vagotomy and pyloroplasty were compared with 77 patients who underwent highly selective vagotomy. A total of 149 patients was followed up for from 1 to 4 years, the average follow-up period being 2·6 years. There was no operative mortality and no significant difference in postoperative morbidity between the two groups. The incidence of recurrent ulceration was greater after highly selective vagotomy, but this difference was not statistically significant. The clinical results were comparable in each group, and although the incidence of diarrhoea and dumping was greater after vagotomy and pyloroplasty, this difference was not statistically significant.

TRUNCAL vagotomy and pyloroplasty (TVP) is currently the operation most commonly performed in the treatment of chronic duodenal ulceration in Great Britain (Johnston and Goligher, 1976). The reported operative mortality is lower than for gastrectomy operations but the recurrent ulcer rate is higher (Goligher et al., 1968).

Highly selective vagotomy (HSV), also described as parietal cell vagotomy or proximal gastric vagotomy, was initially conceived by Griffith and Harkins (1962) and introduced clinically with a drainage procedure by Holle and Hart (1967), and without a drainage procedure by Johnston and Wilkinson (1970) and Amdrup and Jensen (1970).

Amdrup et al. (1974) suggested that HSV gave better clinical results than vagotomy and drainage operations, chiefly by decreasing the incidence of diarrhoea and dumping. They also reported a low recurrent ulcer rate of less than 1 per cent in over 300 patients followed up for 2–4 years in Leeds and Copenhagen, whereas other authors (Grassi et al., 1973; Wastell et al., 1974; Kronborg and Madsen, 1975) have observed a recurrence rate of between 1 and 22 per cent.

Consequently, several trials have been set up to compare HSV with other forms of vagotomy and drainage. A prospective, randomized trial of HSV and TVP in Sheffield (Koffman et al., 1975) showed a recurrent ulcer rate of 2·5 per cent in each group of 40 patients followed up for 1–3 years. There were comparable clinical results but there was significantly more diarrhoea after TVP. Kennedy et al. (1975) reported that HSV produced significantly less dumping, nausea and bile vomiting than selective vagotomy and gastrojejunostomy without an increased risk of recurrent ulcer (2 per cent in each group).

More recently, Amdrup et al. (1977) have compared HSV and selective gastric vagotomy without drainage in a randomized trial in which 267 out of 554 patients were followed up after 2 years. The recurrence rates were 8 per cent in each group and there were similar clinical results, although there was significantly less dumping after HSV. We considered that it was important to carry out a prospective, randomized comparison of the most commonly used operation, TVP, with HSV in a trial encompassing not only teaching hospitals but also district general hospitals.

Patients and methods

Design of the trial

A group of physicians and surgeons from four hospitals in the Manchester area took part in this trial. Both male and female patients undergoing surgery for proved chronic duodenal ulceration were entered into the trial between 1973 and 1976. All patients were assessed preoperatively using a standard questionnaire. Fifty-eight per cent of patients seen during the trial period were excluded for the following reasons.

1. Emergency operation for perforation or bleeding.
2. Pyloric stenosis.
3. Concurrent gastric ulcer.
4. Associated gastrointestinal disease such as biliary tract disease and symptomatic hiatus hernia.
5. Hypergastrinaemia.
6. Either operation not technically feasible at laparotomy.

After the diagnosis of chronic duodenal ulceration had been confirmed at laparotomy, patients were randomly assigned to either HSV or TVP by the drawing of a trial card from a box

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* C. G. Koffman, J. B. Elder, I. E. Gillespie and P. C. Ganguli: University Department of Surgery, Manchester Royal Infirmary. D. G. Ostick, D. J. Cowley, I. W. Dymock and D. E. F. Tweedle: University Department of Surgery, Withington Hospital, Manchester. P. F. Schofield and C. D. R. Pengelly: Park Hospital Davyhulme, Manchester. M. Shafiq and D. R. Shreeve: North Manchester General Hospital. M. Palmer: Department of Statistics, Christie Hospital, Manchester.

Correspondence to: J. B. Elder, University Department of Surgery, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

Table I: COMPARABILITY OF GROUPS

	TVP	HSV	Total
Number	76	77	153
Male	61	63	124
Female	15	14	29
Mean age (yr)	41·3	39·5	

Table II: FOLLOW-UP (1–4 YEARS)

	TVP	HSV
Available	74	75
Dead	1	0
Lost	1	2

Table III: COMPARISON OF IMMEDIATE MORBIDITY AFTER EACH OPERATION

	TVP	HSV
Operative mortality	0	0
Chest infection	16	20
Pulmonary embolus	2	2
Wound infection	6	6
Incisional hernia	3	0
Other complications	1	1
Mean hospital stay (d)	10·7	10·9

Table IV: COMPARISON OF VOLUMES OF RESTING GASTRIC JUICE AT 10 DAYS

	TVP (n = 42),	HSV (n = 41)
Minimum volume (ml)	4·0	0·0
Maximum volume (ml)	849·0	180·0
Mean volume (ml)	119·1	42·4
s.d.	177·0	38·4

Table V: NUMBER OF PATIENTS WITH SUSPECTED AND PROVED RECURRENT ULCER AFTER OPERATION

	TVP (n = 74)	HSV (n = 75)
Suspected	1	3
Proved	2	6
Total	3	9

Table VI: MODIFIED VISICK GRADING 1–4 YEARS AFTER OPERATION

		TVP (n = 74)	HSV (n = 75)
Good	I II	63 (85·1%)	61 (81·4%)
Poor	III IV	11 (14·9%)	14 (18·6%)

kept in the theatre. The two operations were standardized as far as possible. HSV was performed using a technique described by Johnston and Wilkinson (1970), as follows: (*a*) each nerve of Latarjet was identified and vagotomy was begun at approximately 6 cm from the pylorus along the lesser curvature; (*b*) the anterior and posterior leaves of the lesser curvature were divided between the stomach and nerve of Latarjet separately; (*c*) the lower oesophagus was encircled and all vagal fibres surrounding it were divided.

Truncal vagotomy and Heineke–Mickulicz pyloroplasty was standardized in the following way: (*a*) a portion of each vagal trunk was sent for histology; (*b*) the pyloroplasty was made 6–8 cm long and closed in one or two layers with chromic catgut.

The preoperative investigations, operative findings and early postoperative progress were recorded by the surgeons on standard forms. On the tenth postoperative day the volume of fasting gastric juice was measured in 54 per cent of the patients. This included all patients admitted to the trial from one district general hospital and one teaching hospital.

Follow-up was carried out at 1 month by the surgeon, and then at 3, 6 and 12 months and thereafter at 6-monthly intervals by a member of the team who did not know the nature of the operation. A detailed assessment of specific symptoms such as pain diarrhoea and dumping was made and recorded using a standard form. An overall assessment of the clinical result was made independently by one physician using a modified Visick classification: grade 1, an excellent result with no gastrointestinal symptoms; grade 2, some mild symptoms but the patient is happy with the result; grade 3, more severe symptoms causing some disability but still better than the preoperative condition; grade 4, recurrent ulceration or disability as severe as or worse than before the operation for any reason.

All information from the standard form was transferred to punch-cards and analysed by computer, using a package of statistical programmes (Statistical Package for the Social Sciences).

Patients

A total of 153 patients has been entered into the trial and followed up for a minimum of 1 year (*Table I*): 76 patients underwent TVP and 77 HSV. The two groups were comparable in the distribution of age and sex. The preoperative data for the two treatment groups were compared and, of 150 variables tested, only previous perforations and duodenal ulcers in first-degree relatives were significantly more frequent ($P < 0{\cdot}05$) in the HSV group, whereas preoperative bile reflux and bile vomiting were more frequent ($P < 0{\cdot}05$) in the TVP group. This incidence of difference is no more than would be expected by chance alone.

Follow-up

In all, 149 patients were seen for follow-up between 1 and 4 years (mean 2·6 years) after operation (*Table II*). One patient died 4 months postoperatively from myocardial infarction and 3 patients have been lost to follow-up.

Results

Immediate

There was no operative mortality. Chest infections were common after both operations (*Table III*) but the difference was not statistically significant. Sixteen patients had chest infections after TVP, whereas there were 20 after HSV. Two patients from each treatment group had pulmonary emboli, which were recognized clinically. The number of wound infections was the same after each operation, namely 6 patients from each group, but 3 of the patients in the TVP group were found subsequently to have incisional hernias. There were no incisional hernias after HSV.

On the tenth postoperative day 83 patients underwent nasogastric intubation and aspiration of residual gastric juice following an overnight fast. There was a significantly greater residual volume in the TVP group ($P < 0{\cdot}01$) (*Table IV*).

One patient from each treatment group developed other major complications. After TVP 1 patient had a prolonged ileus and after HSV 1 patient had a large gastrointestinal bleed. The mean length of stay in hospital was similar following both operations; 10·7 days after TVP (range 6–19) compared with 10·9 days after HSV (range 5–30).

Long term

Twelve patients had suspected or proved recurrent duodenal ulcers: 9 of these patients were from the HSV group and 3 from the TVP group (*Table V*). The incidence of proved recurrent ulcer after HSV was 8 per cent and after TVP 4 per cent. The proved recurrent ulcers had been identified on barium meal examination and gastroscopy or seen at a second operation. In the suspected group either these investigations had not been performed at the time of writing or the results were equivocal.

An overall assessment of functional results was made using a modified Visick classification. Grades 1 and 2 were considered to be good results and grades 3 and 4 were considered poor (*Table VI*). The results for the two operations were similar: 63 patients were considered to have good results after TVP compared with 61 patients after HSV, whereas 11 and 14 patients respectively had poor results.

Dumping (defined as the presence of two or more of the following symptoms: faintness, sweating, fatigue or fullness after food) was present in 7 patients after TVP compared with 3 patients after HSV. This difference is not statistically significant. All patients were asked about bowel habit, and specifically about the usual character of the stools, the number per week and the patient's impression of bowel habit. If the patient had diarrhoea, further questions were asked about the frequency and length of attacks, the number of motions passed in attacks and whether they were episodic. Five patients complained of diarrhoea after TVP but only 2 patients did so after HSV. When we compared the frequency of bowel habit at *follow-up* with the patient's bowel habit *before* operation we found little difference between the two operations. Although some patients had more frequent bowel action (24 after TVP compared with 18 after HSV), in the majority it was unchanged (40 and 45 patients respectively) and some patients had a less frequent bowel action (10 after TVP and 12 after HSV).

Discussion

This study was designed to compare two operations in uncomplicated duodenal ulceration and therefore required strict conditions for entry. Adherence to the stringent protocol required to achieve this uniformity resulted in the exclusion of 58 per cent of patients undergoing surgery. Randomization resulted in two groups which are very similar in that they are comparable in 146 out of the 150 variables recorded. Four hospitals took part in the trial, two being district general hospitals and two teaching hospitals.

There was no operative mortality and the immediate morbidity after operation was similar in the two groups. There was no statistically significant difference in the incidence of respiratory complications despite operating times 20–100 per cent longer for HSV than for TVP. A possible advantage of HSV is that the gastrointestinal tract is not opened and so wound contamination should not occur. However, the number of wound infections was the same after each operation, although there were 3 patients with incisional hernias after TVP.

One patient had a prolonged ileus with gastric stasis after TVP and it is interesting that we found a significantly larger volume of resting gastric juice after TVP on the tenth postoperative day, although this did not present a serious clinical problem. There have been reports of lesser curve ischaemia and necrosis (Newcombe, 1973; Halvorsen et al., 1975); however, following HSV no patient developed necrosis of the stomach in the present study. One patient did have a large gastrointestinal haemorrhage after HSV, but the cause of this was not established.

The number of patients with proved recurrent duodenal ulceration after HSV is higher than in the non-randomized series reported by Amdrup et al. (1974) but identical to the recent findings of Amdrup et al. (1977) in their randomized trial. The high recurrent ulcer rate reported by Kronborg and Madsen (1975) suggests a basic difference in clearance of the oesophagus, as suggested by Goligher (1974). We found a higher recurrence rate after HSV, although this was not statistically significant. This higher recurrence rate could be due to the limited experience of surgeons in performing the operation of HSV. However, all the principals in the trial had been to Leeds to watch demonstrations of the technique of HSV and had performed the operation during the 12 months before the trial.

According to the modified Visick grading used, 85 per cent patients had good results after TVP and 81 per cent after HSV. These results are similar to those of a smaller Sheffield trial (Koffman et al., 1975) in that there was no statistically significant difference in the number of good results after either operation.

A reduced incidence of both dumping and diarrhoea has been widely reported after HSV compared with TVP (Humphrey et al., 1972; Johnston et al., 1972; Koffman et al., 1975). Our results show a similar trend but in neither case does the difference reach statistical significance. The diarrhoea which patients suffered after TVP was usually episodic but when we compared the frequency of bowel motion before operation and at follow-up there was little difference between the two operations. Further detailed analysis of both preoperative and postoperative symptoms such as diarrhoea and dumping has been made by the Manchester Ulcer Trial Group (Koffman and Ostick, 1978) and will be reported fully in a subsequent paper.

From our results we can conclude that both HSV and TVP are safe operations and relatively free from complications. At this stage our results do not show a significant advantage for either operation with regard to recurrent ulceration, overall clinical results or postoperative diarrhoea and dumping.

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References

AMDRUP E., ANDERSEN D. and HOSTRUP H. (1977) The Aarhus County Vagotomy Trial: interim report. *Scand. J. Gastroenterol.* **12**, Suppl. 45, p. 4.

AMDRUP E. and JENSEN H. E. (1970) Selective vagotomy of the parietal cell mass preserving innervation of the undrained antrum. *Gastroenterology* **59**, 522–527.

AMDRUP E., JENSEN H. E., JOHNSTON D. et al. (1974) Clinical results of parietal cell vagotomy (highly selective vagotomy) two to four years after operation. *Ann. Surg.* **180**, 279–284.

GOLIGHER J. C. (1974) A technique for highly selective (parietal cell or proximal gastric) vagotomy for duodenal ulcer. *Br. J. Surg.* **61**, 337–345.

GOLIGHER J. C., PULVERTAFT C. N., DE DOMBAL F. T. et al. (1968) Five-to-eight-year results of Leeds–York controlled trial of elective surgery for duodenal ulcer. *Br. Med. J.* **2**, 781–787.

GRASSI G., ORRECHIA C., SBUELZ B. et al. (1973) Early results of the treatment of duodenal ulcer by ultraselective vagotomy without drainage. *Su[illegible] Gynecol. Obstet.* **136**, 726–728.

GRIFFITH C. A. and HARKINS H. N. (1962) Selective gastric vagotomy: physiological basis and technique. *Surg. Clin. North Am.* **42**, 1431–1441.

HALVORSEN J. F., HEIMANN P., SOLHAUG J. H. e[illegible]975) Localised avascular necrosis of lesser curv[illegible] complicating highly selective vagotomy [illegible] 590–591.

HOLLE F. and HART W. (1967) Neue Wege der Ch[illegible] des Gastroduodenalulkus. *Med. Klin.* **62**, 441–450.

HUMPHREY C. S., JOHNSTON D., WALKER B. E. et al. (1972) Incidence of dumping after truncal and selective vagotomy with pyloroplasty and highly selective vagotomy without drainage procedure. *Br. Med. J.* **3**, 785–788.

JOHNSTON D. and GOLIGHER J. C. (1976) Selective, highly selective or truncal vagotomy? *Surg. Clin. North Am.* **56**, 1313–1331.

JOHNSTON D., HUMPHREY C. S., WALKER B. E. et al. (1972) Vagotomy without diarrhoea. *Br. Med. J.* **3**, 788–790.

JOHNSTON D. and WILKINSON A. R. (1970) Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer. *Br. J. Surg.* **57**, 289–295.

KENNEDY T., JOHNSTON G. W., M[illegible]RAE K. D. et al. (1975) Proximal gastric vagotomy: interim results of a randomised controlled trial. *Br. Med. J.* **2**, 301–303.

KOFFMAN C. G. and OSTICK D. G. (1978) An assessment of post-vagotomy symptoms in a randomized trial. *Br. J. Surg.* **66**, 814.

KOFFMAN C[illegible] EREZ-AVILA [illegible] DUTHIE H. L. et al. (1975) A con[illegible] omparison [illegible] hly selective vagotomy aga[illegible] uncal vagotomy and pyloroplasty for duodenal ulcer. *Gut* **16**, 829.

KRONBORG O. and MADSEN P. (1975) A [illegible]trolled, randomised trial of highly selective vagotomy versus selective vagotomy and pyloroplasty. *Gut* **16**, 268–271.

NEWCOMBE J. F. (1973) Fatality after highly selective vagotomy. *Br. Med. J.* **1**, 610.

WASTELL C., COLIN J. F. and MCNAUGHTON J. (1974) Proximal gastric vagotomy with and without pyloroplasty—the present position. *Eur. Surg. Res.* **6**, 1–4.

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Interrelations between serum gastrin levels, gastric emptying and acid output before and after proximal gastric vagotomy and truncal vagotomy and antrectomy

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L. K. HARDING [illegible] ALE[illegible]ER-W[illegible] *

SUMMARY

In a prospective study of proximal gastric vagotomy and truncal vagotomy and antrectomy measurements were made, before and after operation, of acid output, gastrin output and gastric emptying of a solid and a liquid meat extract meal. No relationships were demonstrable between acid output and gastrin output. Truncal vagotomy and antrectomy (TVA) produced rapid early emptying of both meals combined with gross prolongation of the overall emptying of the solid meal. Truncal vagotomy and antrectomy reduced the integrated gastrin output after either meal. Proximal gastric vagotomy (PGV) produced rapid early emptying of the liquid meal with no alteration in the early emptying of the solid meal; however, overall solid meal emptying was delayed. Proximal gastric vagotomy increased basal, peak and integrated gastrin output. In preoperative patients slow solid meal emptying was associated with higher gastrin output but after PGV the reverse was found, the slowest emptiers having the lowest gastrin output. These findings do not support the contention that a pyloroplasty should be added to PGV to reduce the hypergastrinaemia produced by the operation.

HOLLE (1974) has stated that proximal gastric vagotomy (PGV) requires the addition of a pyloroplasty in order to rectify the delay produced in the gastric emptying of solid food. The rationale is that higher than normal gastrin levels seen after PGV as opposed to after PGV and pyloroplasty (Jaffe et al., 1974) are due to delayed antral emptying and may stimulate acid output and predispose to recurrent ulceration. To assess the validity of this hypothesis we have measured the relevant physiological indices in a prospective trial of PGV and truncal vagotomy and antrectomy (TVA) in the treatment of duodenal ulceration.

Patients and methods

Twenty-one male patients with radiologically proved duodenal ulceration were randomly allocated for either PGV or TVA with a gastroduodenal anastomosis. Before and 3 months after operation the following studies were performed:

1. Basal acid output (BAO) and the peak acid output to pentagastrin 0·6 μg/kg PAO_{pg}.
2. The gastric emptying of a liquid meal of 400 ml of meat extract solution (40 g meat extract), and of a mixed meal of 400 ml of minced meat, peas, potato and milk. Measurements were made with an external scanning technique using a gamma camera and the meals were labelled with indium 113^m chelated with DTPA. The details of the method have been described elsewhere (Donovan, 1976).
3. Serum gastrin concentrations were measured by the radioimmunoassay method (Jackson et al., 1972) using an antibody which detects G34, G17 and G13. Measurements were made in the fasting state and during the gastric emptying studies at 10, 20, 30, 40, 60 and 90 min after the start of the meal. The integrated gastrin output (IGO) was devised by calculating the area under the curve.

The statistical test used to compare data was the non-parametric Mann–Whitney U test. Where correlations have been attempted, the non-parametric Spearman's ranked correlation has been applied.

Results

The results of the acid output studies are shown in *Table I*. There was no significant difference in the reduction of basal acid output after TVA compared with PGV. However, after TVA the reduction in peak acid output was significantly greater than that seen after PGV ($U = 2·6$, $P<0·01$). After PGV, 6 of the 10 patients still had a PAO_{pg} greater than 20 mmol/h.

The results of the gastrin determinations before and after PGV are shown in *Table II*. Proximal gastric vagotomy significantly raised fasting gastrin ($P<0·05$), peak gastrin (liquid meal $P<0·05$, solid meal $P<0·001$) and the IGO (liquid meal $P<0·05$, solid meal $P<0·01$). The results of the gastrin determinations before and after TVA are shown in *Table III*. Truncal vagotomy and antrectomy had no significant effect on the fasting gastrin level or on the peak response to the solid meal, but the procedure significantly reduced both the peak response to the liquid meal ($P<0·05$) and the IGO (liquid meal $P<0·005$, solid meal $P<0·05$).

The peak gastrin concentration occurred significantly sooner after TVA than before operation ($U = 2·1$, $P<0·05$). After TVA 9 of the 10 peak levels were recorded at the first estimation, 10 min after the meal. There was no significant change in the timing of the peak gastrin concentration after the solid meal following TVA or in the timing of the peak after either meal following PGV.

No significant correlations were found between BAO and fasting gastrin concentration before or after surgery. No significant correlations were found between PAO_{pg} and the IGO of the solid and liquid meals before or after surgery.

The gastric emptying results have been expressed by two indices, the first index being the peak volume of meal attained in the stomach (*Fig.* 1). This is the measurement of early emptying occurring mostly during ingestion of the meal. The lower the peak volume, the greater is the extent of the early emptying. After gastric operations the measurement of early emptying is especially important as a number of authors have described a very rapid early phase of gastric emptying which differs considerably from the later overall exponential pattern (McKelvey, 1970; Cobb et al., 1971; Clarke and Alexander-Williams, 1973; Colmer et al., 1973).

The second index used to define the emptying pattern is the $t_{\frac{1}{2}}$ of the best-fit exponential regression

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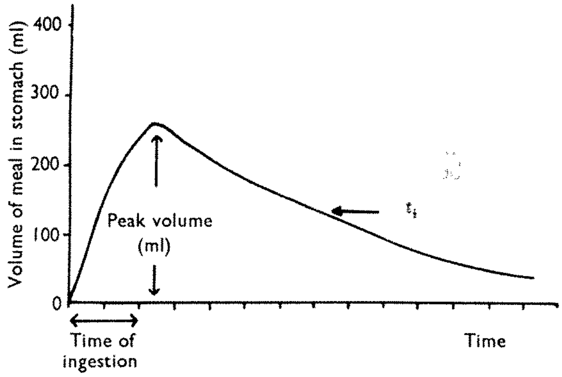

Fig. 1. Interpretation of gastric emptying studies.

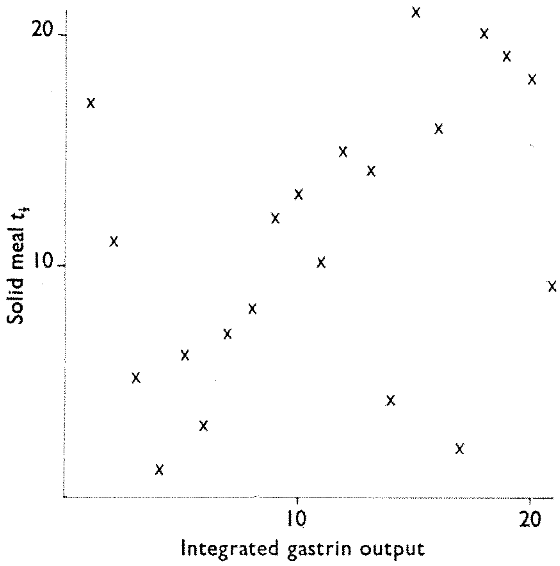

Fig. 2. Spearman ranked correlation of preoperative solid meal $t_{\frac{1}{2}}$ with integrated gastrin output. ($n = 21$, $U = 1{\cdot}84$, $P < 0{\cdot}05$, ρ, 0·414.)

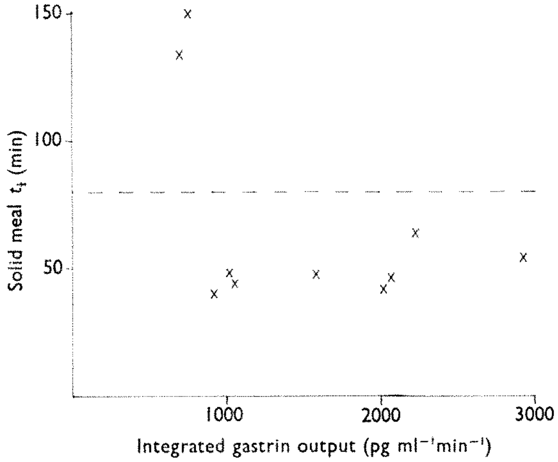

Fig. 3. Solid meal emptying and integrated gastrin output after proximal gastric vagotomy.

Table I: ACID OUTPUT (mmol/h)

		Preop.	Postop.
PGV	BAO	2·5	1·8
	PAO_{pg}	38·5	23·0
TVA	BAO	1·1	0·4
	PAO_{pg}	44·2	2·6

Median values are given.

Table II: SERUM GASTRIN LEVELS BEFORE AND AFTER PGV (pg/ml)

	Preop.	Postop.	*U*	*P*
Fasting	25 (13–51)	47 (20–96)	2·1	<0·05
Peak level				
Meat extract	95 (44–308)	218 (93–534)	1·9	<0·05
Solid meal	119 (51–294)	180 (90–440)	3·2	<0·001
Integrated gastrin output				
Meat extract	606 (218–1437)	1267 (601–3900)	2·2	<0·05
Solid meal	783 (375–1934)	1399 (729–2920)	2·35	<0·01

$n = 10$; values are median and range.

calculated from the stomach volumes from the peak volume onwards (*Fig.* 1). The gastric emptying results before and after PGV are shown in *Table IV.* Proximal gastric vagotomy significantly increased the early emptying of the liquid meal ($P < 0{\cdot}01$) without significantly altering the $t_{\frac{1}{2}}$. Proximal gastric vagotomy had no significant effect on the early emptying of the solid meal but significantly prolonged the $t_{\frac{1}{2}}$ ($P < 0{\cdot}01$). The results before and after TVA are shown in *Table V.* Truncal vagotomy and antrectomy produced a significant increase in the early emptying of the liquid meal with no significant alteration in the $t_{\frac{1}{2}}$. Truncal vagotomy and antrectomy also produced a significant increase in the early emptying of the solid meal with significant prolongation of the $t_{\frac{1}{2}}$. In general, the severity of abnormality produced was greater with TVA than with PGV. The gastric emptying data have been published in full previously (Donovan, 1976).

No significant correlation was found between the $t_{\frac{1}{2}}$ of the liquid meal and its IGO before operation or after PGV or TVA. A significant correlation was demonstrated, however, between the preoperative solid meal $t_{\frac{1}{2}}$ and the associated IGO (*Fig.* 2). The longer $t_{\frac{1}{2}}$s were associated with an increase in IGO ($P < 0{\cdot}05$). After TVA no significant correlation between solid meal $t_{\frac{1}{2}}$ and the IGO was demonstrated. The values after PGV are shown in *Fig.* 3, the broken line representing the upper limit of our normal range for the solid meal $t_{\frac{1}{2}}$. No significant correlation was found. The two patients showing an abnormally long $t_{\frac{1}{2}}$ had the lowest IGO in the group, the reverse of the preoperative trend. In addition, these 2 patients had the lowest PAOs in the PGV group (0 and 0·3 mmol/h respectively).

Discussion

In the preoperative patients the expected relationship between the integrated gastrin output and the rate of solid meal emptying has been demonstrated. After

Table III: SERUM GASTRIN LEVELS BEFORE AND AFTER TVA (pg/ml)

	Preop.	Postop.	*U*	*P*
Fasting	23 (15–131)	26 (13–75)	0·33	n.s.
Peak level				
Meat extract	88 (42–342)	41 (23–95)	2·1	<0·05
Solid meal	100 (41–20[illegible]	55 (16–180)	1·1	n.s.
[illegible]				
[illegible]	45[illegible] ([illegible]–1449)	251 (14·2–566)	2·0	<0·005
[illegible]	[illegible]95 (246–1[illegible]40)	379 (136–687)	1·9	<0·05

$n = 11$; values are median and range.

Table IV: GASTRIC EMPTYING BEFORE AND AFTER PGV

	Preop.	Postop.	*U*	*P*
Liquid meal				
Peak volume	335 (280–395)	255 (190–350)	2·5	<0·01
$t_{\frac{1}{2}}$	21·7 (13·7–43·2)	22·5 (16·2–35·1)	0·15	n.s.
Solid meal				
Peak volume	340 (265–400)	350 (310–380)	0·11	n.s.
$t_{\frac{1}{2}}$	34·9 (16·1–51·4)	46·7 (39·8–150)	2·5	<0·01

$n = 10$; values are median and range.

Table V: GASTRIC EMPTYING BEFORE AND AFTER TVA

	Preop.	Postop.	*U*	*P*
Liquid meal				
Peak volume	340 (215–375)	210 (155–305)	2·7	<0·005
$t_{\frac{1}{2}}$	17·7 (11·3–36·5)	23·6 (5·5–74·2)	1·2	n.s.
Solid meal				
Peak volume	340 (250–370)	320 (265–360)	2·1	<0·05
$t_{\frac{1}{2}}$	38·1 (24·0–80·8)	103 (15·4–446)	2·4	<0·01

$n = 11$; values are median and range.

PGV, however, the normal relationship has altered, delayed emptying being associated with the lowest gastrin outputs in the group. These findings do not support the proposal that the delay produced in the emptying of solid food is a major factor in the production of hypergastrinaemia after PGV. This conclusion is contrary to our own earlier findings using a liquid dextrose meal and a different method of measuring gastric emptying (Jaffe et al., 1974), when we proposed that the lower gastrin levels we found after PGV and pyloroplasty as opposed to PGV reflected the increased rate of emptying produced by the pyloroplasty.

We feel, therefore, that there is no support from our present study for the contention that pyloroplasty should be added to PGV and, as others (Thompson et al., 1976) have stated, the addition of pyloroplasty negates most of the advantages of PGV.

In our present study we found that after PGV there was a slow rise and decline in gastrin levels after stimulation by the meat extract meal despite rapid early gastric emptying and a normal $t_{\frac{1}{2}}$. Five of the 10 patients having had PGV had gastrin levels greater than 90 pg/ml at 90 min from the start of the meal compared with none of the 10 before operation. These findings could, in part, be explained by decreased gastrin metabolism in the denervated gastric fundus, as has been shown in the dog by Evans and his colleagues (1974), or by some other mechanism of prolongation of the half-life of the gastrin. However, in 2 of the 10 patients there was a late secondary rise in gastrin concentration after the meat extract meal, suggesting continued stimulation of antral gastrin release. As there has been no slowing of the rate of emptying of the liquid meal, this finding suggests failure of shut-off of gastrin release. Low acid production would be the obvious mechanism to implicate, but in the 2 patients with the late rise in gastrin levels the PAO_{pg} was 31·0 and 28·8 respectively. It may be that there is some other mechanism for stopping antral gastrin release which is mediated by the innervated gastric fundus.

After TVA the peak gastrin concentration after meat extract stimulus was reached with greater rapidity than before operation. In addition, in 9 of the 11 patients the concentrations returned to basal levels by 20 min after the stimulus. These findings suggest that after TVA there is no prolonged gastrin production as was found after PGV.

After TVA the gastrin response to a meal is presumably short half-life gastrin released from the duodenum. The great prolongation of the $t_{\frac{1}{2}}$ of the solid meals after TVA was associated with an almost 50 per cent reduction in the IGO compared with before the operation, in the presence also of a great reduction in acid inhibition. The ability of the denervated duodenum to produce gastrin upon stimulation would seem, therefore, to be very limited.

References

CLARKE R. J. and ALEXANDER-WILLIAMS J. (1973) The effect of preserving antral innervation and of a pyloroplasty on gastric emptying after vagotomy in man. *Gut* **14**, 300–307.

COBB J. S., BANK S., MARKES I. N. et al. (1971) Gastric emptying after vagotomy and pyloroplasty. *Am. J. Dig. Dis.* **16**, 207–215.

COLMER M. R., OWEN M. G. and SHIELDS R. (1973) Pattern of gastric emptying after vagotomy and pyloroplasty. *Br. Med. J.* **2**, 448–450.

DONOVAN I. A. (1976) The different components of gastric emptying after gastric surgery. *Ann. R. Coll. Surg. Engl.* **58**, 368–372.

EVANS J. C. W., REEDER D. D., BECKER H. D. et al. (1974) Extraction of circulating endogenous gastrin by the gastric fundus. *Gut* **15**, 112–115.

HOLLE F. (1974) In: HOLLE F. and ANDERSON S. (ed.) *Vagotomy: Latest Advances*. Berlin, Springer-Verlag, p. 124.

JACKSON B. M., REEDER D. D. and THOMPSON J. C. (1972) Dynamic characteristics of gastrin release. *Am. J. Surg.* **123**, 137–142.

JAFFE B. M., CLENDINNEN B. G., CLARKE R. J. et al. (1974) Effect of selective and proximal gastric vagotomy on serum gastrin. *Gastroenterology* **66**, 944–954.

MCKELVEY S. T. D. (1970) Gastric incontinence and post-vagotomy diarrhoea. *Br. J. Surg.* **57**, 741–742.

THOMPSON J. C., FENDER H. R., WATSON L. C. et al. (1976) The effects on gastrin and gastric secretion of five current operations for duodenal ulcer. *Ann. Surg.* **183**, 599–608.

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Scalp and cranial substitution with autotransplanted greater omentum using microvascular anastomosis

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AND R. C. KESTER*

SUMMARY
A case is described whereby a large defect of scalp and cranium was successfully covered using autotransplanted greater omentum, revascularized by microsurgical techniques.

THE methods of covering large surface defects in man have been revolutionized by use of a free flap of skin and subcutaneous tissue which is immediately revascularized by microsurgical anastomoses. When Goldwyn et al. (1963) first transposed such skin flaps to distant sites in the dog, a new era of surgical reconstruction was introduced. Using the operating microscope, the technique of anastomosing arteries and veins of about 1 mm in diameter was first established in the animal laboratory (Krizek et al., 1965; Strauch and Murray, 1967; Fujino et al., 1972) and then applied to the clinical situation. The first successful microvascular flap operation in man was carried out in September 1972 by Harii et al. (1974). Such microvascular operations are now commonplace in many centres specializing in reconstructive surgery.

We wish to describe a case whereby an extensive defect of the scalp and skull was covered by transferred greater omentum, which was immediately revascularized by microvascular anastomosis.

Case report

The patient, a woman born in 1913, had a rodent ulcer of the right frontal scalp treated by radium needle implants in 1939. She suffered a local recurrence in April 1949 which was treated by excision and skin grafting. The graft failed in the central area and therefore, in October 1949, at Leeds, the ulcerated lesion and the underlying outer table of skull were excised. The defect was covered by a scalp transposition flap. Histology of the specimen showed an inflammatory reaction with no evidence of malignancy.

A further recurrence of basal cell cancer in 1954 was treated by local excision and skin grafting. A larger recurrence was observed in 1960, but the patient refused to undergo treatment. This lesion was eventually excised in December 1963. The defect was repaired by an acromiopectoral tube pedicle which had been prepared by seven operations between August and November 1963. The patient remained clinically free of tumour until the end of 1965, when a lesion in the left supraorbital region was discovered. This recurrence was widely excised in February 1966, removing the supra-orbital ridge. The defect was repaired with an abdominal marsupial flap which had been prepared over the previous 12 weeks by eight operations.

Between 1966 and 1972 nine further scalp lesions were excised. Histological examination confirmed multi-focal basal cell cancer with complete removal on each occasion. In January 1973 a large left frontal parasagittal recurrence was excised. A preoperative carotid angiogram had shown a partial occlusion of the sagittal sinus just anterior to its mid-point. The tumour was seen to be infiltrating the underlying bone and a 9 × 7 cm flap of bone was excised. The tumour had infiltrated the dura and the sagittal sinus and two cortical drainage veins were sacrificed to enable most of it to be removed. A complete excision would have necessitated clipping a third large drainage vein on the dominant hemisphere and ligation of the sagittal sinus and its mid-point with risk of consequent bifrontal infarction. The excised dura was replaced with cadaver dural graft. The scalp and cranial defect was covered by a further abdominal marsupial flap which had been prepared over 3 months by six operations. The patient declined postoperative radiotherapy. During the succeeding 3 years, multiple small recurrences in the scalp skin flaps were excised, including one deeper lesion.

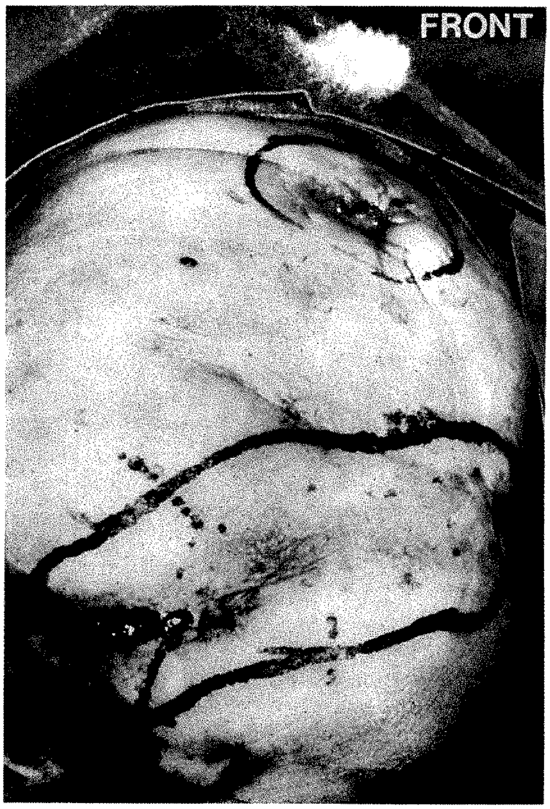

Fig. 1. Recurrences of basal cell cancer within the anterior and posterior aspects of the scalp are encircled.

In September 1976 the patient presented with two large recurrences in the scalp overlying the anterior and posterior limits of the previous craniectomy (*Fig.* 1). An electroencephalogram showed abnormal slow wave activity over the left frontal area and a computerized axial tomograph confirmed suspicions of a further extension of the parasagittal tumour in lateral and inferior directions. It was decided that extensive excision of the recurrence was indicated and that the large scalp and cranial defect would be best substituted by a free omental graft which would be revascularized by microsurgical techniques.

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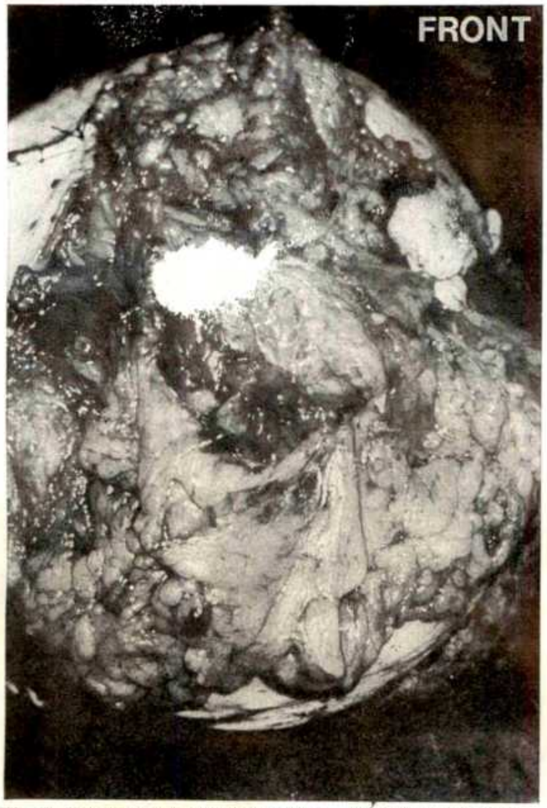


Fig. 2. Vascularized omental graft covering the scalp and cranial defect.

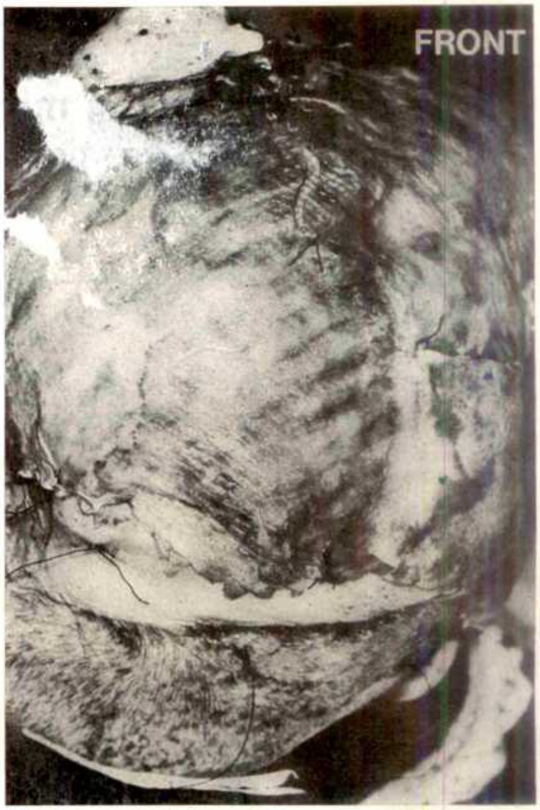


Fig. 3. Viable split skin grafts covering the omentum 2 weeks postoperatively.

Omental transfer operation (30 March 1977)

Excision of the skin and further underlying skull containing macroscopic recurrences of basal cell cancer was performed, leaving a skin defect of 17 × 12 cm and a bone defect of 12 × 9 cm. The anterior recurrence was fully excised along that part of the involved sagittal sinus and falx. The large posterior recurrence extended along the falx on both sides to a depth of 4 cm and was 3 cm in diameter, displacing but not invading the cerebral cortex. This lesion could again not be completely removed without the risk of venous infarction. All the infiltrated dura was excised and the defects were repaired with bovine dural grafts (Ethicon Ltd). The right superficial temporal artery and vein were dissected to provide recipient vessels for the free omental graft.

Through a transverse supra-umbilical incision, the greater omentum was dissected and removed from the transverse colon and the greater curvature of the stomach, preserving the right gastroepiploic vessels. The diameters of the vein and artery were about 2 mm and 1 mm respectively. Anastomosis of the superficial temporal to the gastroepiploic vessels was accomplished with a Zeiss OPMI Mark VIII operating microscope which provided zoom magnification from × 10 to × 40. The vessel ends were irrigated with heparinized saline. Interrupted Ethilon 10/0 sutures (Ethicon Ltd) were used, anastomosing first the veins (with 12 sutures) and then the arteries (with 10 sutures). The omental graft was ischaemic for about 1·5 h. Following release of the microvascular clamps, revascularization of the omentum was immediate and satisfactory and it was now plicated to cover the defect (*Fig.* 2). The surface of the omentum was next covered by split skin grafts taken from the thighs. The total operating time for the three teams of surgeons was about 11 h. Postoperatively, the patient made an uneventful recovery; the skin grafts took completely (*Fig.* 3) and she was discharged 3 weeks after operation. Six months later she had a further small superficial basal cell cancer excised from the lower occipital scalp. At 15 months after omental grafting atrophy of the omental pad is barely perceptible and the skin grafts remain healthy.

Discussion

Omentum was first transposed as a free autotransplant, using microvascular anastomosis, by McLean and Buncke (1972) to cover the denuded skull following resection of the scalp for malignancy. The left gastroepiploic vessels of the graft were anastomosed to the superficial temporal vessels with the aid of the operating microscope. Several further microvascular transfers of greater omentum to the head have been reported (Harii and Ohmori, 1973; Ikuta, 1975; Sykes, 1975). Omental transplantation by microvascular anastomosis has been used to cover the brachial plexus to alleviate incapacitating neuritis (Clodius, 1974) and to reconstruct facial atrophy (Harii, 1975; O'Brien, 1977).

As the fan-shaped cribriform mass of omentum is highly conformable and easy to work with, it readily fills irregular defects. The well-vascularized rays of fat can be pleated and refolded upon themselves without jeopardizing the blood supply, to provide a thick, protective buffer. Split skin grafts laid upon the omental cushion have an excellent chance of a successful 'take'. We are not aware of any case in which a thick vascularized omental pad has been employed to substitute cranial bone in addition to scalp tissue. Such an omental transfer operation proved highly acceptable to our patient because of the convenience and reduced hospitalization time, in contrast to her previous experiences with tube pedicle and marsupial flap repairs.

References

CLODIUS L. (1974) Symposium on Microsurgery, New York. Quoted in O'BRIEN (1977).

FUJINO T., HARASHINA T. and MIKATO A. (1972) Autogenous en bloc transplantation of the mammary gland in dogs, using microsurgical technique. *Plast. Reconstr. Surg.* **50**, 376–381.

GOLDWYN R. M., LAMB D. L. and WHITE W. L. (1963) An experimental study of large island flaps in dogs. *Plast. Reconstr. Surg.* **31**, 528–536.

HARII K. (1975) Sixth International Congress of Plastic and Reconstructive Surgery, Paris. Quoted in O'BRIEN (1977).

HARII K. and OHMORI S. (1973) Use of the gastroepiploic vessels as recipient or donor vessels in the free transfer of composite flaps by microvascular anastomoses. *Plast. Reconstr. Surg.* **52**, 541–548.

HARII K., OHMORI K. and OHMORI S. (1974) Hair transplantation with free scalp flaps. *Plast. Reconstr. Surg.* **53**, 410–413.

IKUTA Y. (1975) Autotransplant of omentum to cover large denudation of the scalp. *Plast. Reconstr. Surg.* **55**, 490–493.

KRIZEK T. J., TANI R., DESPREZ J. D. et al. (1965) Experimental transplantation of composite grafts by microsurgical vascular techniques. *Plast. Reconstr. Surg.* **36**, 538–546.

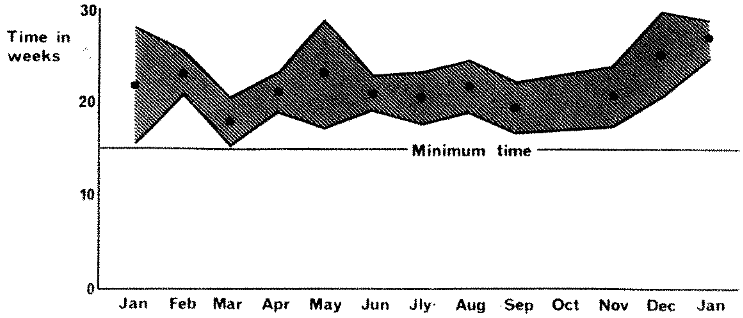
MCLEAN B. H. and BUNCKE H. J. (1972) Autotransplant of omentum to a large scalp defect, with microsurgical revascularisation. *Plast. Reconstr. Surg.* **49**, 268–274.

O'BRIEN B. M. (1977) *Microvascular Reconstructive Surgery*. Edinburgh, Churchill Livingstone, p. 236.

STRAUCH B. and MURRAY D. E. (1967) Transfer of a composite graft with immediate suture anastomosis of its vascular pedicle measuring less than 1 mm in external diameter using microsurgical techniques. *Plast. Reconstr. Surg.* **40**, 325–329.

SYKES P. J. (1975) In: O'BRIEN B. M. *Microvascular Reconstructive Surgery*. Edinburgh, Churchill Livingstone, p. 235.

Paper accepted 15 August 1978.



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Non-occlusive acute intestinal vascular failure

ULF HAGLUND AND OVE LUNDGREN*

SUMMARY

The records of 87 patients with vascular intestinal insufficiency leading to gangrene were analysed in retrospect. In 77 patients the cause of the vascular insufficiency could be determined. In 25 per cent no organic obstruction to blood flow was found in the macroscopic intestinal vessels. The patients with non-occlusive intestinal gangrene showed a tendency to be younger and to have associated cardiac infarction more frequently than those with vessel obstructions. Moreover, non-occlusive intestinal gangrene was found more frequently following a period of systemic arterial hypotension. A history of atrial fibrillation and digitalis therapy was present with equal frequency in both groups of patients.

Based on these cases and on current animal experimental data, it is suggested that the bowel gangrene seen in non-occlusive ischaemia is due to short-circuiting of oxygen at the base of the villi in the villous counter-current exchanger. This mechanism becomes much more effective in hypotension owing to reduced velocity of the villous blood flow. The possibility is emphasized that, with a coexisting atherosclerotic narrowing in the mesenteric vascular tree, cardiovascular disturbances which are themselves not enough to alter central arterial pressure, may none the less induce regional hypotension. Such regional hypotension could lead to villous destruction and initiate a vicious circle which ends in generalized gangrene of the bowel.

INTESTINAL gangrene in the presence of a patent arterial tree has been called 'non-occlusive intestinal ischaemia' and appears to be increasing in frequency over the past two decades (Jackson, 1963; Williams, 1971). The outcome is almost invariably fatal (Williams, 1971; Lancinault and Jacobson, 1976). The cause of non-occlusive intestinal ischaemia is largely unknown, but inadequate cardiac response to minor increases in functional demand, coupled with visceral atherosclerosis, is believed to be of great importance.

The present retrospective investigation was carried out to elucidate whether the previously proposed causative factors, such as age, cardiovascular disease, hypotension and digitalis medication, were distributed in a different way in patients with non-occlusive intestinal ischaemia as compared with patients with gangrene due to intestinal arterial obstruction. Based on the results of this retrospective study and on the experimental data obtained in our laboratory, a hypothesis concerning the pathogenesis of non-occlusive intestinal ischaemia is presented.

Patients and methods

The records from 87 consecutive patients with intestinal gangrene due to acute vascular insufficiency treated between 1971 and 1975 at Sahlgren's Hospital, Göteborg, were analysed. In all cases the diagnosis was confirmed at laparotomy and/or post-mortem examination. The cause of the intestinal infarction, and in most cases the diagnosis of the associated diseases, was obtained from autopsy protocols and/or from examination of resected specimens. In 10 patients (11 per cent) no such investigation was performed and hence the cause of the intestinal gangrene was unknown. *Table I* shows the cause of intestinal gangrene in the remaining 77 patients.

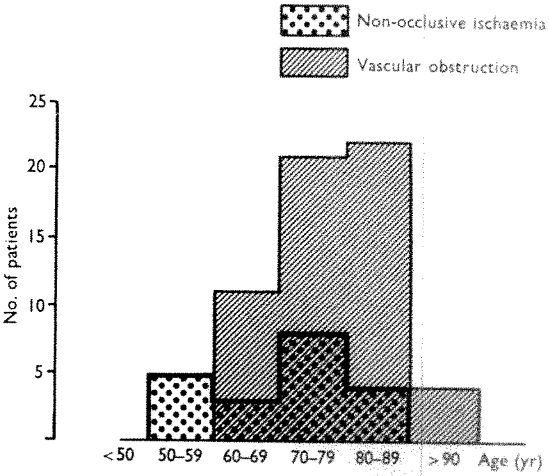

Fig. 1. The age distribution of the patients with non-occlusive intestinal ischaemia and of those with macroscopic obstruction to the intestinal blood flow.

Table I: CAUSES OF INTESTINAL GANGRENE

	No.		%	
Non-occlusive ischaemia	19		25	
Arterial embolus	34	49	44	64
Arterial thrombosis	15		19	
Venous thrombosis	6		8	
Dissecting aortic aneurysm	3		4	
Total	77		100	

In comparing the different groups the χ^2 test was used (Siegel, 1956). Thirty-four (39 per cent) of the 87 patients were men: 9 (47 per cent) of the 19 patients with non-occlusive disease were men as were 20 (41 per cent) of the 49 patients with arterial vascular occlusion (not significant).

In *Fig.* 1 the age distribution in the group with intestinal gangrene secondary to obstructive vascular disease ($n = 58$) is compared with that in the group with patent vessels ($n = 19$). The patients with non-occlusive intestinal ischaemia were on average about 10 years younger than those with vessel obstruction. Eight (42 per cent) of the non-occlusive cases were under 70 years of age compared with only 11 (19 per cent) of the patients in the group with obstruction ($P < 0{\cdot}05$).

Associated diseases

Eleven patients (58 per cent) with non-occlusive intestinal ischaemia had known grave cardiovascular diseases compared with 46 (79 per cent) of the 58 patients with vascular obstruction (n.s.) and 64 (74 per cent) of the total material (n.s.). Atrial fibrillation was found to be equally common in the different groups; thus, it was present at the time of admission in 30 (52 per cent) of the 58 patients with vascular obstruction and in 20 (59 per cent) of the 34 with superior mesenteric artery emboli. Eight (49 per cent) of the non-occlusive patients had atrial fibrillation.

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Table II: OPERATIVE PROCEDURES

	No occlusion	Arterial obstruction	Total case series
No operation			
No. of cases	9	34	46
No. of survivors	—	—	—
Exploratory laparotomy			
No. of cases	4	[illegible]	20
No. of survivors	—	—	—
Embolectomy with or without resection			
No. of cases	—	3	4
No. of survivors	—	—	—
Resection of < 200 cm of intestine			
No. of cases	4	4	12
No. of survivors	1	2	6
Resection of > 200 cm of intestine			
No. of cases	2	2	5
No. of survivors	1	—	1

Cardiac infarction was diagnosed before the onset of the abdominal symptoms in 5 (26 per cent) of the non-occlusive and in 6 (10 per cent) of the cases with intestinal vascular obstruction ($P<0{\cdot}10$). A significant period of arterial hypotension was found in 8 (42 per cent) of the non-occlusive group and in 3 (5 per cent) of the vascular obstruction group ($P<0{\cdot}05$). The cause of the arterial hypotension in the non-occlusive group was: cardiogenic (3 cases), dehydration (2 cases), postoperative hypovolaemia (1 case) and in 2 cases with significant dehydration it was not possible in retrospect to determine the exact cause. In the group with vascular obstruction the hypotension was cardiogenic in 2 cases and secondary to haemorrhage due to fractures in 1 case.

Thirteen (68 per cent) of the non-occlusive and 45 (78 per cent) of the arterial obstruction patients were on digitalis therapy at the time of the onset of the abdominal symptoms (n.s.).

Survival rate

In the non-occlusive group 2 patients (11 per cent) survived compared with 5 (9 per cent) in the occlusive group (n.s.). None of the patients where the pathogenesis remains unknown survived. Two of the 6 patients with venous thrombosis survived as did 1 of the 3 with dissecting aortic aneurysms and 2 of the 49 patients with acute arterial obstruction. The overall survival was thus 8 per cent. At the time when the clinical diagnosis was definite or sufficiently obvious to indicate laparotomy, 9 (47 per cent) of the non-occlusive group, 25 (43 per cent) of the 58 patients in the occlusive group and 42 (48 per cent) of the total had clinical signs of diffuse peritonitis and/or shock. In 24 patients (28 per cent) the disease was found to be too advanced and no active treatment except analgesics was given and 10 additional patients (11 per cent) died during the period of preoperative substitution therapy. In 7 (37 per cent) of the non-occlusive group and in 5 (9 per cent) ($P<0{\cdot}05$) of the group with vascular obstruction the diagnosis was made unexpectedly at post-mortem when, on clinical grounds, the cause of death had been thought to lie outside the abdomen.

Operative procedure

Table II illustrates the operative procedures performed, related to the diagnosis and the outcome. As already stated, only 41 of the 87 patients (47 per cent) were operated upon and, moreover, in 20 of them (23 per cent) only an exploratory laparotomy was performed. In 6 of the 7 surviving patients only a limited part of the intestine was affected and a resection of the gangrenous area was performed. In the seventh survivor the major part of the small intestine was resected and a jejunoileal anastomosis carried out.

Discussion

The present retrospective investigation was carried out in a group of 77 patients with intestinal infarction, in whom a thorough pathological investigation of the cause had been performed. In 19 patients (25 per cent) no obstruction to blood flow was found, as far as could be judged from inspection of the intestinal vessels. If anything, this frequency is less than would be expected from previous studies (Liavåg, 1967; Williams, 1971; Marston, 1977). Venous vascular occlusion was found in 8 per cent of patients, which is within the accepted range (Williams, 1971). The proportion of patients having intestinal infarction due to venous occlusion seems to have declined over the past 20 years (Jackson, 1963; Williams, 1971). The mortality rate in our 87 patients with intestinal gangrene was 92 per cent which is similar to that reported previously (Mavor et al., 1963; Liavåg, 1967; Williams, 1971). In the group of patients consisting of cases 'treated' conservatively or subjected only to an exploratory laparotomy ($n = 66$), the mortality was 100 per cent, as in other series (Mavor et al., 1963; Liavåg, 1967; Williams, 1971). On the other hand, 7 (33 per cent) of the 21 patients treated surgically, by resection of the devitalized part of the intestines, survived. In this, as in earlier series, the high mortality was largely due to the fact that the disease was diagnosed or suspected too late—in one-half of the cases at a time when diffuse peritonitis and/or shock was present.

Pathogenesis

Most studies of non-occlusive intestinal ischaemia have been performed on autopsy material. Although some patients may develop non-occlusive intestinal ischaemia without any obvious precipitating factor (Glotzer and Shaw, 1959; Blennerhassett and Reid, 1960; Williams, 1971), most of the reported patients have had severe cardiac failure with or without infarction (Ende, 1958; Glotzer and Shaw, 1959; Blennerhassett and Reid, 1960; Ming and Levitan, 1960; Mösslacher and Slany, 1972; Aldrete et al., 1977), or arterial hypotension and shock from other causes (Blennerhassett and Reid, 1960; Williams et al., 1967; Williams, 1971; Wiklund et al., 1976). Advanced age and digitalis medication are other important features (Williams, 1971; Renton, 1972; Lancinault and Jacobson, 1976). The current concept of pathogenesis is that increasing cardiovascular demands in these old and atherosclerotic patients leads to a failure of intestinal perfusion, due to redistribution of blood flow from the splanchnic area secondary to sympathetic activity and/or other agents causing intestinal vasoconstriction, such as digitalis (Williams, 1971; Renton, 1972; Lancinault and Jacobson, 1976). The chain of events alone, and even more so in the presence of arterial stenosis, results in ischaemia of the mucosa (Williams, 1971; Lancinault and Jacobson, 1976).

In the present study the patients with non-occlusive intestinal ischaemia were, on the whole, younger ($P<0{\cdot}05$) and had a higher incidence of myocardial infarction ($P<0{\cdot}10$) than those with blocked vessels. No significant difference was found in this study in the frequency of associated cardiovascular disease and digitalis medication between the non-occlusive patients and those with macroscopic vessel obstruction. On the other hand, non-occlusive ischaemia appeared to occur significantly more frequently secondary to a period of arterial hypotension ($P<0{\cdot}05$).

These observations are in agreement with the hypothesis that the most important factor precipitating

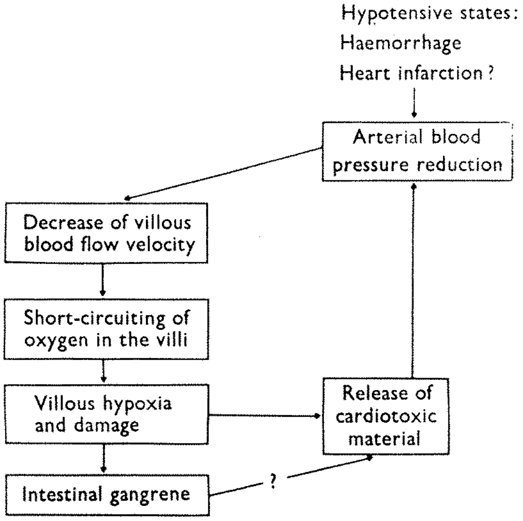
Hypotensive states:
Haemorrhage
Heart infarction?
Arterial blood pressure reduction
Decrease of villous blood flow velocity
Short-circuiting of oxygen in the villi
Villous hypoxia and damage
Release of cardiotoxic material
Intestinal gangrene
?

Fig. 2. The suggested 'vicious circle', illustrating the importance of intestinal mucosal lesions in hypotensive states in the development of shock.

non-occlusive ischaemia is a reduction of the intestinal perfusion pressure, however caused. It has been demonstrated in cats that a reduction of the intestinal perfusion pressure great enough to lower intestinal blood flow to 30–50 per cent of its resting value induces mucosal infarction within 2 h (Haglund et al., 1976a), and this experimental model is considered to resemble closely the clinical situation in non-occlusive intestinal ischaemia. In the experimental animal the mucosal damage first appears at the villous tip (Chiu et al., 1970; Åhrén and Haglund, 1973), which also seems to be the starting point in intestinal gangrene in humans (Williams, 1971; Marston, 1977). Although total intestinal blood flow is only moderately reduced, the hypoxic nature of the villous damage has been demonstrated (Åhrén and Haglund, 1973; Haglund et al., 1976a; Shute, 1976). Moreover, in hypotension severe enough to reduce total intestinal blood flow to 30–50 per cent in the experimental animal, the volume of blood supplying the villi is almost unchanged, although the velocity of flow in the villi is much reduced (Lundgren and Svanvik, 1973). This paradox, whereby hypoxia pronounced enough to cause tissue death within 2 h occurs in spite of an unchanged blood supply, can be explained by the extravascular short-circuiting of oxygen at the base of the villi in the villous counter-current exchanger (Lundgren, 1967; Kampp et al., 1968; Lundgren and Haglund, 1978). The villus is supplied with blood by a central arteriole and a subepithelial set of venous vessels, constructed so that the arterial and the venous blood flow in opposite directions. The distance between the two limbs of the villous vascular exchanger is less than 20 μm, which allows a significant amount of extravascular 'shunting' of oxygen in the exchanger, even during normal 'resting' conditions (Kampp et al., 1968). A four- to fivefold reduction of the villous blood flow velocity, which has been shown to occur in the cat in hypotension, without significant reduction of villous blood flow, would increase the effectiveness of the counter-current exchange mechanism considerably. In this situation the villous tips may become anoxic in spite of an unchanged blood volume supply (Åhrén and Haglund, 1973; Haglund et al., 1976a; Lundgren and Haglund, 1978). Once the mucosal damage has developed, a vicious circle is created, since the damaged intestinal tissue apparently releases toxic substances with a negative inotropic effect on the heart. This tends to intensify the hypotension, as illustrated schematically in *Fig.* 2 (Haglund and Lundgren, 1973; Haglund et al., 1976b; Lundgren et al., 1976; Haglund et al., 1978).

As mentioned above, it is generally accepted that the intestinal damage seen in non-occlusive intestinal vascular failure starts with mucosal infarction (Williams, 1971; Whitehead, 1972; Marston, 1977). The hypothesis proposed is that the mucosal damage is caused by extravascular short-circuiting of oxygen due to reduced intestinal perfusion pressure. The steps involved in, and the time course of, the development from mucosal to total bowel wall infarction are not yet known in all details. The progressive cardiovascular deterioration induced by the mucosal damage (*Fig.* 2) is certainly of importance in inducing a further reduction of the blood flow to the muscle layer. Local release of proteolytic enzymes (Haglund et al., 1977) and increased permeability to toxic substances and bacteria from the lumen and from the infarcted mucosa (Bounous et al., 1966) may also be of importance.

The pathogenic mechanism proposed above was further substantiated by the experimental finding that the same mucosal lesions developed in cats subjected to hypotension and continuous vasoconstrictor nerve stimulation as in those in which the small intestine had been denervated (Haglund and Lundgren, 1977).

A significantly high proportion of our patients with non-occlusive vascular insufficiency had an episode of hypotension before the clinical signs of gangrene developed. However, in those who did not have a recorded period of low arterial blood pressure it is quite possible that a slight and unnoticed fall in pressure, due (for example) to cardiac infarction, atrial fibrillation or dehydration, may have preceded the clinical signs. Such a small reduction of the pressure head can be enough to reduce intestinal perfusion pressure significantly, decreasing villous blood flow velocity and, thus, inducing villous damage. This possibility is supported by the frequent finding of atherosclerotic narrowing of the visceral arteries in unselected autopsy material (Derrick et al., 1959; Marston, 1977). The pressure gradients caused by such lesions can amount to 75 mmHg or more (Stoney and Wylie, 1966; Kiser and Utley, 1968). Hence, a drop in systemic blood pressure which clinically would not be named 'hypotension' may, in a patient at risk, damage the small bowel mucosa. The clinical hypotension may in turn be the result of release of cardiotoxic substances from the ischaemic mucosa (*Fig.* 2).

In the present series, resection of the involved intestine was the only treatment that saved life, regardless of the type of intestinal vascular insufficiency. However, this procedure could only be performed in a minority of the patients, mainly because of delay in diagnosis, in line with what has been found in most other reported series (Mavor et al., 1963; Williams, 1971; Marston, 1977). Other methods of treatment have, however, been described. In non-occlusive intestinal ischaemia early diagnosis by selective angiography followed by regional intra-arterial infusion of substances such as papaverine and phenoxybenzamine has been reported as successful in single cases (Boley et al., 1973; Athanasoulis et al., 1975; Lancinault and Jacobson, 1976). In arterial obstruction, surgical procedures such as embolectomy, thromboendarterectomy and bypass operations have been successfully carried out on a few patients (Marston, 1977). However, these reports are all based on a small series and 25 years after the first successful superior mesenteric artery embolectomy (Klass, 1951) the high mortality in acute intestinal vascular insufficiency has hardly fallen, if at all.

Our experimental experience on the feline small bowel suggests that treatment with intravenous administration of methylprednisolone (Haglund et al., 1976a, b) or a β_1-stimulating drug, or alternatively the intestinal instillation of an albumin solution (Haglund et al., 1976a, b), may be worth trying in patients with threatened non-occlusive intestinal vascular failure.

Acknowledgement

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References

ÅHRÉN C. and HAGLUND U. (1973) Mucosal lesions in the small intestine of the cat during low flow. *Acta Physiol. Scand.* **88**, 541–550.

ALDRETE J. A., HAN S. Y., LAWS H. L. et al. (1977) Intestinal infarction complicating low cardiac output states. *Surg. Gynecol. Obstet.* **144**, 371–375.

ATHANASOULIS C. A., WITTENBERG J., BERNSTEIN R. et al. (1975) Vasodilatory drugs in the management of non-occlusive bowel ischaemia. *Gastroenterology* **68**, 146–150.

BLENNERHASSETT J. B. and REID J. D. (1960) Intestinal infarction: with particular reference to cases occurring without macroscopic occlusion of vessels. *N.Z. Med. J.* **59**, 131–138.

BOLEY S. J., SPRAYREGEN S., VEITH F. J. et al. (1973) An aggressive roentgenologic and surgical approach to acute mesenteric ischaemia. *Surg. Ann.* **5**, 355–378.

BOUNOUS G., MCARDLE A. H., HODGES D. M. et al. (1966) Biosynthesis of intestinal mucin in shock: relationship to tryptic hemorrhagic enteritis and permeability to curare. *Ann. Surg.* **164**, 13–22.

CHIU C.-J., MCARDLE A. H., BROWN R. et al. (1970) Intestinal mucosal lesion in low flow states. I. A morphological, hemodynamic and metabolic reappraisal. *Arch. Surg.* **101**, 478–483.

DERRICK J. R., POLLARD H. S. and MOORE R. M. (1959) The pattern of arteriosclerotic narrowing of the celiac and superior mesenteric arteries. *Ann. Surg.* **149**, 684–689.

ENDE N. (1958) Infarction of the bowel in cardiac failure. *N. Engl. J. Med.* **258**, 879–881.

GLOTZER D. J. and SHAW R. S. (1959) Massive bowel infarction. *N. Engl. J. Med.* **260**, 162–167.

HAGLUND U. (1973) The small intestine in hypotension and hemorrhage. An experimental cardiovascular study in the cat. *Acta Physiol. Scand.* Suppl. 387.

HAGLUND U., ABE T., ÅHRÉN C. et al. (1976a) The intestinal mucosal lesions in shock. I. Studies on the pathogenesis. *Eur. Surg. Res.* **8**, 435–447.

HAGLUND U., ABE T., ÅHRÉN C. et al. (1976b) The intestinal mucosal lesions in shock. II. The relationship between mucosal lesions and the cardiovascular derangement following regional shock. *Eur. Surg. Res.* **8**, 448–460.

HAGLUND U. and LUNDGREN O. (1973) Cardiovascular effects of bloodborne material released from the cat small intestine during simulated shock conditions. *Acta Physiol. Scand.* **89**, 558–570.

HAGLUND U. and LUNDGREN O. (1977) The significance of sympathetic nervous activity for the development of the intestinal mucosal lesions in shock. *Acta Chir. Scand.* **143**, 139–143.

HAGLUND U., LUNDHOLM K., LUNDGREN O. et al. (1977) Intestinal lysosomal enzyme activity in regional simulated shock: influence of methylprednisolone and albumin. *Circ. Shock* **4**, 27–34.

HAGLUND U., MYRVOLD H. and LUNDGREN O. (1978) Studies on cardiac and pulmonary function in simulated intestinal shock. *Arch. Surg.* **113**, 963–969.

JACKSON B. B. (1963) *Occlusion of the Superior Mesenteric Artery.* Springfield, Ill., Thomas.

KAMPP M., LUNDGREN O. and NILSSON N. J. (1968) Extravascular shunting of oxygen in the small intestine of the cat. *Acta Physiol. Scand.* **72**, 396–403.

KISER J. L. and UTLEY J. R. (1968) Visceral artery reconstruction. *Am. J. Surg.* **116**, 720–724.

KLASS A. A. (1951) Embolectomy in acute mesenteric occlusion. *Ann. Surg.* **134**, 913.

LANCINAULT G. and JACOBSON E. D. (1976) The gastrointestinal circulation. *Gastroenterology* **71**, 851–873.

LIAVÅG I. (1967) Acute mesenteric vascular insufficiency. *Acta Chir. Scand.* **133**, 631–639.

LUNDREN O. (1967) Studies on blood flow distribution and countercurrent exchange in the small intestine. *Acta Physiol. Scand.* Suppl. 303.

LUNDGREN O. and HAGLUND U. (1978) The pathophysiology of the intestional counter-current exchanger. *Life Sci.* **23**, 1411–1422.

LUNDGREN O., HAGLUND U., ISAKSSON O et al. (1976) Effects on myocardial contractility of blood-borne material released from the feline small intestine in simulated shock. *Circ. Res.* **38**, 307–315.

LUNDGREN O. and SVANVIK J. (1973) Mucosal hemodynamics in the small intestine of the cat during reduced perfusion pressure. *Acta Physiol. Scand.* **88**, 551–563.

MARSTON A. (1977) *Intestinal Ischaemia.* London, Arnold.

MAVOR G. E., LYALL A. D., CHRYSTAL K. M. R. et al. (1963) Mesenteric infarction as a vascular emergency. The clinical problems. *Br. J. Surg.* **50**, 219–225.

MING S.-C. and LEVITAN R. (1960) Acute hemorrhagic necrosis of the gastrointestinal tract. *N. Engl. J. Med.* **263**, 59–65.

MÖSSLACHER H. and SLANY J. (1972) Funktionelle hämorrhagische Infarzierung des Darmes bei Herzeninsuffizienz. *Wien. Z. Inn. Med.* **53**, 277–282.

RENTON C. J. C. (1972) Non-occlusive intestinal infarction. *Clin. Gastroenterol.* **1**, 655–673.

SHUTE K. (1976) Effect of intraluminal oxygen on experimental ischaemia of the intestine. *Gut* **17**, 1001–1006.

SIEGEL S. (1956) *Nonparametric Statistics for the Behavioral Sciences.* New York, McGraw-Hill.

STONEY R. J. and WYLIC E. J. (1966) Recognition and surgical management of visceral ischaemic syndromes. *Ann. Surg.* **164**, 714–721.

WHITEHEAD R. (1972) The pathology of intestinal ischaemia. *Clin. Gastroenterol.* **1**, 613–637.

WIKLUND L., GREVSTEN S., NILSSON F. et al. (1976) Non-occlusive enteric gangrene associated with severe upper gastrointestinal bleeding. *Acta Chir. Scand.* **142**, 593–597.

WILLIAMS L. F. (1971) Vascular insufficiency of the intestine. *Gastroenterology* **61**, 757–777.

WILLIAMS L. F., ANASTASIA L. F., HASIOTIS C. A. et al. (1967) Non-occlusive mesenteric infarction. *Am. J. Surg.* **114**, 376–381.

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Changing pattern in aetiology of pancreatitis in an urban Swedish area

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SUMMARY

Two groups of patients admitted with a first attack of acute pancreatitis are reviewed. The first group, consisting of 105 patients, was admitted between 1968 and 1969; the second group of 204 patients was admitted between 1974 and 1975. These groups were compared with one of 454 patients admitted between 1956 and 1960 whose details were published earlier by our unit (Edlund et al., 1968). The aim of this study was to determine whether the incidence of factors associated with pancreatitis within the population of the city of Göteborg had changed in the 20-year period. In the 1956–60 group gallstone disease was the main associated factor (68 per cent), but in the later groups alcohol-induced pancreatitis assumed the leading role (68 and 66 per cent respectively). Alcohol-induced pancreatitis tended to occur at a younger age than gallstone pancreatitis. Thirty-one per cent of 449 patients admitted with an acute attack of alcoholic pancreatitis in the two last periods of study had had previous attacks.

THE association between pancreatitis and either gallstone disease or alcoholism is well documented. Up to a decade ago, gallstone disease was commonly implicated (Bockus et al., 1955; Richman, 1956; Howard and Jordan, 1960; Edlund et al., 1968). In some recent reports from Britain gallstone disease still predominates (Imrie and Blumgart, 1975; Imrie and Whyte, 1975; Read et al., 1976). Recently, however, an increased incidence of alcohol-induced pancreatitis has been reported. In 1972 Kager et al. in Stockholm reported a high incidence of alcoholism among male patients with acute pancreatitis. Similar reports have come from the USA (Olsen, 1974; Ranson et al., 1974; Ranson et al., 1976). A rise in the incidence of alcohol-related acute pancreatitis has been reported from Denmark (Lindahl and Røder, 1976; Madsen, 1976) and also from Britain, where alcoholism has so far been uncommon as a cause (Gillespie, 1973; Imrie, 1974; Trapnell and Duncan, 1975).

The aim of the present study was to determine whether the incidence of associated factors in patients admitted to Sahlgren's Hospital with an acute attack of pancreatitis had changed during three separate periods over 20 years. The patient population is that of a university teaching hospital which handles all emergency cases in the area. The relative incidence of factors may thus represent the true proportion in this region of Sweden. We wanted to know if there had been a changing pattern in the aetiology of pancreatitis in the city of Göteborg, with a population of approximately 450 000 inhabitants, during 20 years. There have been only slight changes of the population during this period.

Patients and methods

Two groups of patients were studied retrospectively. The first 155 patients were admitted between 1968 and 1969; 105 of these patients suffered a first attack and 50 had had previous attacks. The second group of 294 patients was admitted between 1974 and 1975; 204 of these were admitted with a first attack and the remaining 90 patients had suffered previous attacks.

In the first group, 18 patients with a first attack were diagnosed either at laparotomy or at autopsy and in the second group 27 patients were similarly diagnosed. In most cases the diagnosis was based upon clinical findings and supported by an increased urinary amylase activity. Those patients suffering a first attack were compared with a similar group of 454 patients who had been admitted between 1956 and 1960 (Edlund et al., 1968).

Patients were divided into three categories depending on associated factors:

1. Gallstone disease.
2. Alcohol overconsumption.
3. Neither gallstone disease nor alcohol abuse.

In the first category either gallstones or a non-functioning gallbladder had been demonstrated at oral cholecystography. In the second category approximately 50 per cent of the patients were heavy drinkers suffering social consequences of their alcoholism. Patients with postoperative pancreatitis were excluded from the study.

Most patients suffered either mild or moderate pancreatitis. Seventeen patients in the 1968–9 group and 21 patients in the 1974–5 group were considered to have severe disease. The treatment of all patients with mild or moderate pancreatitis over the 20-year period was uniformly conservative without the use of specific drugs. Laparotomy was performed on a few patients where the diagnosis was doubtful. Six patients with severe pancreatitis in the 1974–5 group were treated with peritoneal dialysis.

Patients with a first attack

Aetiology: There was a significant difference between the aetiological factors associated with the 1956–60 group and those associated with the two later groups (*Table I*). In 1956–60 gallstone disease was a factor in 310 out of 454 patients (68 per cent), whereas alcohol-induced pancreatitis accounted for only 65 patients (14 per cent). In the 1968–9 group alcohol-induced pancreatitis assumed a leading role, accounting for 71 out of 105 patients (68 per cent) and gallstone disease accounted for only 21 patients (20 per cent). This changing trend from gallstone-induced to alcohol-induced pancreatitis is confirmed in the 1974–5 group, where 135 out of 204 patients (66 per cent) were alcoholics and only 54 patients (26 per cent) had gallstones. *Fig.* 1 illustrates this changing pattern in the aetiology of pancreatitis in intervals of 10 and 5 years.

Age and sex: In the 1956–60 group there were as many women as men, but in the later groups there was a higher male incidence: 83 per cent in the 1968–9 group and 77 per cent in the 1974–5 group (*Table II*). Alcoholic pancreatitis occurred at a younger age (*Fig.* 2); thus although 33 per cent of patients were under the age of 40 in the 1956–60 series, 49 per cent were noted in the 1974–5 group. Patients with gallstone pancreatitis, however, tended to be older in the last period of study.

In the later groups there was also a higher incidence of women with alcoholic pancreatitis. Thus, 14 women were included in this category in the last period compared with a combined total of 3 in the two earlier periods. In patients with gallstone pancreatitis the sex incidence was equal in all three groups.

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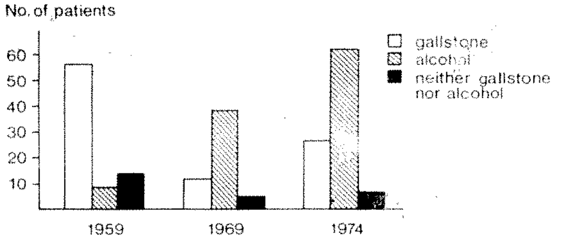

Fig. 1. Associated factors in patients with a first attack of pancreatitis in intervals of 10 and 5 years.

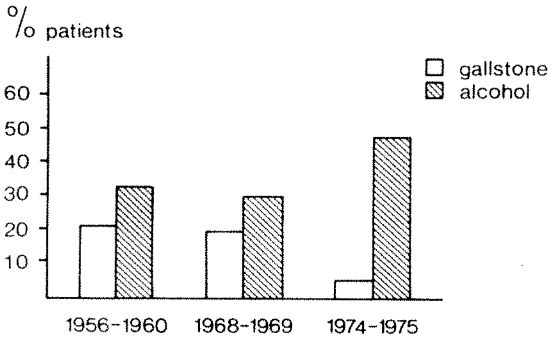

Fig. 2. Percentage of patients up to 40 years of age with a first attack of gallstone or alcoholic pancreatitis.

Mortality: The mortality in the 1974–5 group was 3 per cent as compared with 8 per cent in the 1956–60 group and 12 per cent in the 1968–9 group. Over the years there has been a reduction in the mortality rate in patients with alcohol-induced pancreatitis (*Table III*). Although 11 per cent died in the 1956–60 group only 1 per cent died in the 1974–5 group. Eleven of 14 patients with alcoholic pancreatitis who died were under 50; none of the other 3 was over 70; but most of the patients who died with gallstone pancreatitis were elderly (23 of 34 patients were over the age of 70). In the 1974–5 group 3 out of 4 patients were over 80.

Patients with previous attacks

It is common for patients with alcohol-induced pancreatitis to relapse (*Table IV*). A total of 332 patients with alcohol-induced pancreatitis were admitted in the last two groups. Of these 38 per cent (126) had had previous attacks requiring admission. Patients with recurrent alcoholic pancreatitis require a shorter mean hospitalization time than those with a first attack (89 per cent *v.* 65 per cent, less than 1 week). There was no mortality among those with recurrences.

Table I: ASSOCIATED FACTORS

	Gallstone (%)	Alcohol (%)	Neither (%)
1956–60	68	14	18
1968–9	20	68	12
1974–5	26	66	8

Table II: SEX INCIDENCE

	Total (no.)	Male (%)	Female (%)
1956–60	454	53	47
1968–9	105	83	17
1974–5	204	77	23

Table III: MORTALITY VERSUS AETIOLOGY

	Gallstone		Alcohol		Neither	
	No.	%	No.	%	No.	%
1956–60	24	8	7	11	5	6
1968–9	6	29	5	7	2	15
1974–5	4	7	2	1	1	7

Table IV: PATIENTS WITH FIRST AND PREVIOUS ATTACKS ADMITTED IN 1968–9 AND 1974–5

	1968–9		1974–5	
	First attack	Previous attacks	First attack	Previous attacks
Gallstone	21	2	54	2
Alcohol	71	45	135	81
Neither	13	3	15	7
Total	105	50	204	90

Discussion

The diagnosis of acute pancreatitis is difficult to establish clinically and there must be possibilities for error in our series. An alcoholic gastritis with elevated amylase activity may mimic an acute pancreatitis leading to overdiagnosis. A raised serum or urine amylase activity may occur in patients with biliary colic with a transient calculous obstruction of the common duct. This may result in an overdiagnosis of pancreatitis in patients with gallstone disease (Millbourn, 1941; Strömbeck, 1947; Sanchez-Ubeda et al., 1956; Bernhard et al., 1959; Adams et al., 1968).

In the male population over 15 years of age in Göteborg we have found an incidence of alcoholic pancreatitis of approximately 0·40 per thousand in 1975 as compared to 0·08 per thousand in 1960. It is also noted that increasingly younger men are becoming affected. There has also been an increase among females.

The use of alcohol in Sweden is now common among young people and those addicted have increased their consumption. The increase of patients with alcoholic pancreatitis observed in our study may be a result of this. A similar observation has been reported from Stockholm (Kager et al., 1972), where alcohol was found to play a dominant role in acute pancreatitis.

We have found the mortality rate following a first attack of alcohol-induced pancreatitis to be significant and younger people tend to be affected. The mortality is negligible, however, during a relapse. These findings are similar to those of Ranson et al. (1974) and Trapnell and Duncan (1975).

The incidence of gallstone-induced pancreatitis has decreased. Although stricter diagnostic criteria may have contributed to this decrease, we believe that the decrease is real. A possible explanation for this may be the widespread modern practice of early cholecystectomy, providing a prophylaxis against pancreatitis. However, older patients with gallstone disease are often not operated upon because of intercurrent disease. This may be the reason for the greater age of the group of patients suffering from gallstone pancreatitis. It may also provide an explanation for the relatively high mortality among this group compared with the patients with alcoholic pancreatitis.

References

ADAMS J. J., LIBERTINO J. A. and SCHWARTZ S. I. (1968) Significance of an elevated serum amylase. *Surgery* **63**, 877–884.

BERNHARD H. R., CRISCIONE J. R. and MOYER C. A. (1959) The pathologic significance of the serum amylase concentration. *Arch. Surg.* **79**, 157–162.

BOCKUS H. L., KALSER M. H., ROTH J. L. et al. (1955) Clinical features of acute inflammation of the pancreas; analysis of 84 attacks in 78 patients. *Arch. Intern. Med.* **96**, 308–321.

EDLUND Y., NORBÄCK B. and RISHOLM L. (1968) Acute pancreatitis, etiology and prevention of recurrence. Follow-up study of 188 patients. *Rev. Surg.* **25**, 153–157.

GILLESPIE W. J. (1973) Observations on acute pancreatitis. A retrospective clinical study. *Br. J. Surg.* **60**, 63–65.

HOWARD J. M. and JORDAN G. L. (1960) *Surgical Diseases of the Pancreas*. Philadelphia, Lippincott.

IMRIE C. W. (1974) Observations on acute pancreatitis. *Br. J. Surg.* **61**, 539–544.

IMRIE C. W. and BLUMGART L. H. (1975) Acute pancreatitis: a prospective study on some factors in mortality. *Bull. Soc. Int. Chir.* **6**, 601–603.

IMRIE C. W. and WHYTE A. S. (1975) A prospective study of acute pancreatitis. *Br. J. Surg.* **62**, 490–494.

KAGER L., LINDBERG S. and ÅGREN G. (1972) Alcohol consumption and acute pancreatitis in men. *Scand. J. Gastroenterol.* **7**, Suppl. 15.

LINDAHL F. and RØDER O. (1976) The pattern of acute pancreatitis. A retrospective study of 163 patients 1971–1976. *Scand. J. Gastroenterol.* **11**, Suppl. 38, p. 14 (Abstr.).

MADSEN O. G. (1976) Acute pancreatitis—follow-up 5–14 years. *Scand. J. Gastroenterol.* **11**, Suppl. 38, p. 15 (Abstr.).

MILLBOURN E. (1941) Klinische Studien über die Choledocholithiasis. *Acta Chir. Scand.* **86**, Suppl. 65.

OLSEN H. (1974) Pancreatitis. A prospective clinical evaluation of 100 cases and review of the literature. *Am. J. Dig. Dis.* **19**, 1077–1090.

RANSON J. H. C., RIFKIND K. M., ROSES D. F. et al. (1974) Prognostic signs and the role of operative management in acute pancreatitis. *Surg. Gynecol. Obstet.* **136**, 69–81.

RANSON J. H. C., RIFKIND K. M. and TURNER J. W. (1976) Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis. *Surg. Gynecol. Obstet.* **143**, 209–219.

READ G., BRAGANZA J. M. and HOWAT H. T. (1976) Pancreatitis: a retrospective study. *Gut* **17**, 945–952.

RICHMAN A. (1956) Acute pancreatitis. *Am. J. Med.* **21**, 246–274.

SANCHEZ-UBEDA R., ROUSSELOT M. and GIANNELLI S. (1956) The significance of pancreatitis accompanying acute cholecystitis. *Ann. Surg.* **144**, 44–50.

STRÖMBECK J. P. (1947) Increased amylase concentration in urine as a sign of choledocholithiasis and acute pancreatic disease. *Acta Med. Scand.* Suppl. 196, pp. 411–418.

TRAPNELL J. E. and DUNCAN E. H. L. (1975) Patterns of incidence in acute pancreatitis. *Br. Med. J.* **2**, 179–183.

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Notice

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The British Journal of Surgery Society Ltd has agreed to reimburse the authors of accepted reviews for their expenses, up to a maximum of £50.

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The role of grey scale ultrasonography in the investigation of jaundice

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SUMMARY

Sixty-seven patients were prospectively studied using grey scale ultrasound (GSU) to assess its possible role as part of a jaundice investigation programme. All scans were performed by one radiologist, without clinical information. When intrahepatic ductal dilatation was found an attempt was made to establish the level and cause of obstruction. The calibre of the intrahepatic bile ducts was correctly reported in 66 patients (98 per cent). Forty-three proved to have extrahepatic cholestasis, 24 had intrahepatic cholestasis. No patient with intrahepatic cholestasis had dilated ducts seen on ultrasound.

In 43 patients with obstructive jaundice, GSU accurately detected the level of obstruction in 28. This accuracy varied with the cause of obstruction. A direct indication of diagnosis was possible in 45 of the 67 patients.

In a unit specializing in the management of complicated hepatobiliary problems, GSU has been shown to be accurate in differentiating extra- from intrahepatic jaundice. Being non-invasive, it appears ideally suited for use as a screening procedure, permitting selection of appropriate invasive investigations to provide complete preoperative imaging of the biliary tree. In patients with jaundice due to gallstones, GSU may be the only imaging technique required before surgery provided good operative cholangiography is available.

THE investigative techniques of percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP) and liver biopsy are now available to aid clinicians in differentiating extra- from intrahepatic causes of jaundice. The justification for using procedures such as PTC and ERCP is that they can provide an accurate preoperative anatomical delineation of the obstructing lesion; if there is no ductal dilatation or obstruction shown, unnecessary 'diagnostic' laparotomy is avoided. Although the morbidity associated with the use of these techniques is low in expert hands, it would be preferable if they could be selected for use in specific groups of patients by a reliable non-invasive screening procedure. Indeed, in his review of cholangiography in the jaundiced patient, Elias (1976) suggested that ultrasound might permit selection of the most appropriate of the standard techniques—PTC, ERCP or liver biopsy—in the individual patient.

The initial success reported in using ultrasound scanning to differentiate extra- from intrahepatic jaundice (Taylor and Carpenter, 1974a) has been supported by subsequent more detailed studies (Neiman and Mintzer, 1977; Taylor and Rosenfield, 1977; Vicary et al., 1977). The purpose of the present study was to assess the role of ultrasound scanning as part of a jaundice-investigation programme. Our specific aims were to establish the reliability of GSU in (*a*) detecting the presence or absence of intrahepatic biliary duct dilatation; (*b*) demonstrating the level of obstruction; and (*c*) demonstrating the cause of obstruction.

Patients and methods

Sixty-seven patients were studied prospectively in Glasgow Royal Infirmary during a 15-month period ending in December 1977. The patients studied fall into two groups. Group 1, a consecutive series of 45 patients with jaundice referred to one surgical unit. In these patients the jaundice was thought to be extrahepatic or had developed following surgery performed elsewhere. Group 2, 22 patients who were initially investigated by physicians in Glasgow Royal Infirmary or elsewhere having presented with a history and clinical findings suggestive of intrahepatic cholestasis. In each case they were seen in consultation since, on the basis of clinical presentation and relevant biochemistry, an obstructive lesion could not be positively excluded.

The patients were not fasted or prepared in any specific way before the scanning. All the investigations were performed by a single consultant radiologist (J. G. D.) who was unaware of the clinical diagnosis, and was asked to determine the presence or absence of dilated intrahepatic bile ducts. In patients with dilated ducts he went on to try to establish the level and cause of the obstruction. All the patients were scanned using a Nuclear Enterprises Diasonograph NE 4200 and had a preliminary plain film of the abdomen taken with a marker placed over the umbilicus so that the presence and site of bowel gas could be identified.

Patients were examined in the supine position. Before commencing the scanning procedure the patients were taught to distend the abdomen, particularly the lower abdomen, during inspiration. Scans were performed following this manoeuvre with respiration suspended. Routine longitudinal scans were performed starting in the midline and subsequently at 0·5-cm intervals to approximately 6 cm to the right to include the head and body of the pancreas, liver hilum and gallbladder area. A 2·5-mHz transducer was used, routinely angled as steeply as possible under the costal margin, and a single sweep scan was performed. The common hepatic and bile ducts were identified most readily by performing a longitudinal radial scan with the transducer angled medially 20–35° to the vertical and also angled 5–10° lateral to the longitudinal plane (*Fig.* 1). Scans were then performed at 0·25–0·5-cm intervals to identify the extrahepatic bile ducts and neck and body of the gallbladder (*Fig.* 2). Transverse or oblique scans were performed as required.

Intrahepatic bile ducts are not normally identified on liver scanning. Dilated intrahepatic ducts are seen as short segments of fine linear or curvilinear tubules particularly in the right lobe of liver. The segments seldom measure more than 8 mm in length on the two-fifths scale and have a clearly identifiable lumen of 0·05 mm or more in diameter. In some instances, they may appear as isolated structures, e.g. when associated with local obstruction due to a hepatic mass or masses. The normal common hepatic duct may be seen lying adjacent to the portal vein on the radial scan as fine parallel lines. The normal common bile duct may be identified at a lower level, sometimes within the head of the pancreas. The commonest cause of failure to obtain a satisfactory scan was gas and faecal matter in the bowel obscuring the lower liver margin and the presence of gas in the first and second parts of the duodenum may obscure the cystic and common bile duct areas.

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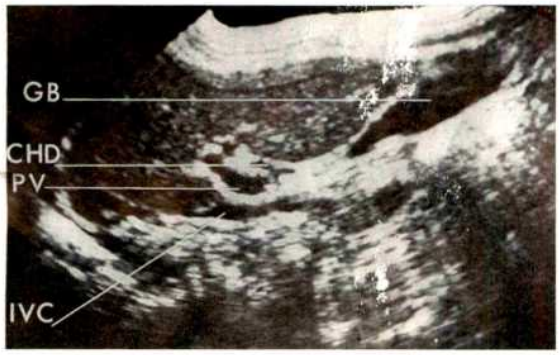

Fig. 1. Longitudinal scan of 56-year-old patient showing: GB, gallbladder containing no gallstones; CHD, common hepatic duct; PV, portal vein; and IVC, inferior vena cava.

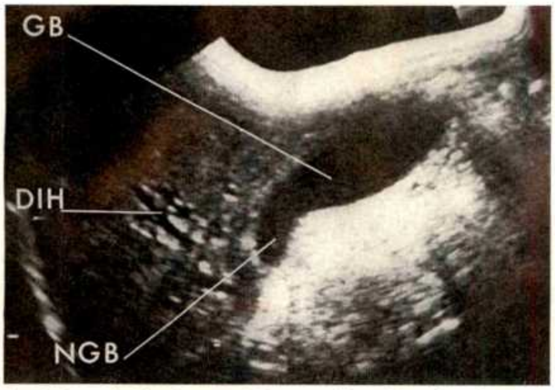

Fig. 2. Longitudinal scan of 64-year-old patient showing: GB, dilated gallbladder containing no gall stones; DIH, dilated intrahepatic ducts; and NGB, neck of gallbladder.

In each patient the ultrasound findings were confirmed by subsequent percutaneous endoscopic or operative cholangiography.

Results

Intrahepatic duct dilatation

In 67 jaundiced patients, dilated intrahepatic ducts were reported in 42 patients and non-dilated in 24 (*Table I*). In only 1 patient was the calibre of the ducts not identified, and this was because the liver could not be adequately visualized on scanning. There were no false positive results for dilatation in either group and no false negative results in group 2. The overall accuracy of GSU in predicting the presence or absence of dilated intrahepatic ducts was thus 98 per cent.

Level of obstruction

Forty-three of the 67 patients proved to have extrahepatic cholestasis (*Table II*). Ultrasound scanning indicated the level of obstruction in 28 of these 43 patients. The accuracy of prediction varied depending on the cause of obstruction. In only 11 of the 20 patients with gallstone disease was the level detected (*Table II*). However, in 7 of the 10 patients with malignant obstruction the level of obstruction was identified, and in all but one patient in the post-cholecystectomy group, the level of obstruction was seen at the time of scanning. The remaining 7 patients had different causes for their jaundice, including liver metastases, carcinoma of the gallbladder and chronic pancreatitis, and in 5 of the 7, the level of obstruction was correctly indicated by ultrasonic cholangiography.

Table I: INTRAHEPATIC DUCT DILATATION

Ultrasound findings		Cholangiography/ operative findings
Dilated ducts	42	42
Non-dilated ducts	24	24
Ducts not identified	1	Dilated

Overall accuracy 98 per cent.

Table II: LEVEL OF OBSTRUCTION

Diagnosis	No. of patients	Level indicated by ultrasound
Gallstones	20	11
Pancreatic carcinoma	10	7
Post-cholecystectomy	6	5
Miscellaneous	7	5

Table III: GALLSTONES (24 PATIENTS)

Ultrasound findings		Cholangiography/ operative findings
Dilated ducts	20	20
Non-dilated ducts	4	4
Gallstones in gallbladder	22	24
Gallstones in gallbladder and common bile duct	2	13

Table IV: MISCELLANEOUS

Ultrasound findings		Final diagnosis	
Dilated ducts	7		
Filling defects in liver	3	Liver metastases	3
Large, solitary filling defect	1	Primary hepatoma	1
Dilated intrahepatic ducts, dilated gallbladder containing debris	1	Carcinoma gallbladder	1
Dilated intrahepatic ducts and dilated gallbladder	1	Chronic pancreatitis	1
Irregular nodules in liver parenchyma	1	Haemangioendothelioma	1
Non-dilated ducts	20		
Normal liver scan or parenchymal abnormality only	18	Alcoholic cirrhosis	6
		Drug-induced cirrhosis	5
		Viral hepatitis	3
		Chronic active hepatitis	1
		Unknown	3
Filling defects	2	Liver metastases	2

Cause of jaundice

Gallstone disease: In 22 of the 24 patients with gallstone disease, gallstones were identified by ultrasound. In the remaining 2 patients the calibre of the intrahepatic bile ducts was correctly reported, but the gallbladder was obscured by intestinal gas and no comment could be made on the presence of gallstones (*Table III*).

At the time of subsequent operation, 11 patients were found to have gallstones only in the gallbladder and in all but one case these had been reported by the ultrasonographer. Of these 11 patients, 9 had dilated intrahepatic bile ducts and 4 also had a dilated common bile duct seen at the time of ultrasound scanning.

Thirteen patients had stones both in [illegible]adder and the common bile duct at the time [illegible]sequent surgery. In 12 of the 13, gallstones were identified in the gallbladder by ultrasound but in only 2 patients were common bile duct stones specifically reported.

Among the 24 patients with gallstones, 4 had an additional pathological diagnosis as a potential cause of jaundice. Two patients had gallstones with no bile duct dilatation and subsequent liver biopsy showed them to have chronic active hepatitis and primary biliary cirrhosis respectively. One patient with known alcoholic cirrhosis developed jaundice and was shown by ultrasound to have a gallstone in the left hepatic duct causing intrahepatic duct dilatation. The fourth patient had dilated ducts and gallstones detected by ultrasonography; subsequent duodenoscopy performed for gastrointestinal haemorrhage revealed an ampullary carcinoma not detected by ultrasound.

Carcinoma of the head of the pancreas: In 10 patients the cause of jaundice was malignant obstruction at the lower end of the common bile duct. Eight patients had a carcinoma of the head of the pancreas or of the periampullary region and 2 patients had ampullary carcinoma. In one patient no view of the intrahepatic ducts was obtained by ultrasound and this patient was subsequently shown to have a carcinoma of the head of the pancreas (*Table I*). Of the remaining 7 patients with a carcinoma of the head of the pancreas, a pancreatic mass was detected by the ultrasonographer in 5 cases, a mass was suspected in a further case and the pancreas could not be identified on scanning in the last patient. No periampullary abnormality was reported by ultrasound in the 2 patients with ampullary carcinoma.

Post-cholecystectomy damage to the common bile duct: Six patients were referred after iatrogenic damage to the common bile duct following surgery performed elsewhere. In 5 of the 6 patients in this group the level of obstruction was identified by the ultrasonographer (*Table II*) and in none of these cases was any extrinsic mass or other cause for the obstruction identified by scanning. The diagnosis of iatrogenic bile duct damage was thus made by exclusion. In the remaining patient, intrahepatic bile duct dilatation was noted but the common bile duct was not identified and so the cause of obstruction could not be indicated.

Miscellaneous: The remaining 27 patients had a variety of causes for their jaundice (*Table IV*). The presence or absence of intrahepatic ductal dilatation was correctly indicated by ultrasound in all 27 patients and the additional detail available indicated the final diagnosis in many cases.

Discussion

The results of this study confirm that GSU scanning is a reliable, non-invasive means of differentiating between intra- and extrahepatic causes of jaundice. It can therefore be used to select the appropriate invasive investigation for each patient, and we would advocate its use at an early stage in the investigation of the jaundiced patient. A high degree of accuracy in separating intra- from extrahepatic causes of jaundice is possible by history taking, clinical examination and liver function tests. Although the level of alkaline phosphatase, particularly taken in relation to the level of the serum transaminases, is probably the best of the commonly used liver function tests in differentiating extrahepatic obstruction from hepatocellular disease there is a non-specific pattern in up to 40 per cent of patients (Stern et al., 1973) and this has been our experience. While our results show ultrasound to be highly reliable in detecting the calibre of the intrahepatic bile ducts, it is of advantage to the surgeon to know both the level and cause of obstruction, and it is important to establish how accurately ultrasound can provide this detailed information.

In our hands the ability of ultrasound to indicate the level of obstruction is dependent to a large degree on the cause of obstruction. Twenty-four of our patients had gallstone disease, of whom 13 had gallstones in the common bile duct at the time of surgery; in only 2 patients were these specifically detected by ultrasound. These results are similar to the experience of other workers, and in their recent report on 150 jaundiced patients, Taylor and Rosenfield were able to identify only 3 of 21 common bile duct stones (Taylor and Rosenfield, 1977). In a similar study reported by Vallon et al. (1978), 5 of 14 common bile duct stones were detected. These results are somewhat disappointing since gallstone disease is the commonest cause of jaundice in patients referred to the surgeon. In most patients with gallstones ultrasound will give the cause of the jaundice, but will often be unable to establish the exact level of obstruction. Difficulty in defining gallstones in the common bile duct is largely due to the fact that no fluid–calculus interface is readily identifiable. Although the stone may produce an echo pattern, it cannot be separately identified from surrounding soft tissue structures.

Patients with gallstone disease present two further problems. First, ultrasound scanning may show gallstones in the gallbladder plus common bile duct dilatation, suggesting gallstone obstruction at the lower end of the duct. By the time of surgery, however, the duct may be shown to be of normal calibre and contain no gallstones. This situation arose in 4 of our patients, and since the dilatation extended below the cystic duct one must postulate that a gallstone has caused obstruction and then passed through the papilla before surgery. Certainly there is strong evidence that stones passed in this way are a frequent cause of acute pancreatitis (McCutcheon, 1968). Secondly, gallstones may be present yet not be responsible for the jaundice; 4 of our patients had such a 'double pathology'. Three of the 4 patients came to surgery on the basis of their clinical presentation, but in the remaining patient the gallstones were thought to be an incidental finding in a patient with chronic active hepatitis and she has not undergone operation.

In patients with pancreatic or ampullary carcinoma, the obstructing lesion usually causes distension of the gallbladder, and one would therefore anticipate that ultrasound would be more successful in detecting the level of obstruction. This proved to be the case in our own series, with the level being indicated by the ultrasonographer in 7 of the 9 patients in whom an adequate scan was obtained. Experience on the ability of ultrasound to detect a pancreatic mass in such patients has been extremely variable. Vicary et al. (1977) reported visualization of a mass in only 25 per cent of cases, this success being similar to that achieved by Taylor and his colleagues (1974b). However, these results are in contrast to a recently reported study by Lees et al. (1978) in which they were able to identify pancreatic carcinoma in 100 per cent of patients examined by GSU. In patients with carcinoma of the head of the pancreas, we were able to identify a definite mass in 70 per cent.

If ultrasound is to be used as a screening procedure to differentiate extrahepatic cholestasis, then it must also be reliable in detecting a normal, non-dilated biliary tree. In all our patients reported by ultrasonic cholangiography to have non-dilated bile ducts, this was confirmed by subsequent investigation. It is important to note that when each of these patients was seen before ultrasonography an obstructive lesion could not be excluded. In previous years a number of these patients might well have come to unnecessary diagnostic laparotomy.

As previously reported, it has been our aim to achieve an early and accurate diagnosis in all jaundiced patients (Blumgart, 1978), and the purpose of this study was to determine the place ultrasound should have in our jaundice investigation programme. Several recent reports have attempted to evaluate the roles of the various investigative techniques, and the exact place of ultrasound, PTC and ERCP will vary from unit to unit, depending both on the type of patient being investigated and on the availability and reliability of the techniques in any one centre. GSU is not available in all hospitals and its successful use is very much dependent on the skill and experience of the operator. All our patients were scanned by a single consultant radiologist who has not only devised an individual technique for outlining the biliary tract, but has also been routinely scanning patients with gallstone disease and acute pancreatitis for several years (McKay et al., 1977; McKay et al., 1978). It is of interest that some erroneous reports have arisen in our own hospital, when the scanning was performed by a less experienced person.

While it could be argued that the reliability of PTC in detecting dilated intrahepatic bile ducts justifies its use in all jaundiced patients, our results suggest that when gallstones and dilated ducts are identified by ultrasonography, one could justifiably proceed straight to surgery. One must be certain that the gallstones are the sole cause of obstruction, and we would recommend that where there is any doubt on clinical or radiological grounds simple duodenoscopy should precede surgery. Gallstones in the common bile duct—which in our hands cannot be positively identified by ultrasound—should be detected by operative cholangiography provided a high quality service is available in theatre.

In patients shown to have non-dilated ducts and gallstones, further investigation is required; if the clinical findings and ultrasound appearance of the liver suggest hepatocellular jaundice then liver biopsy is indicated. Some of these patients will have a history suggesting biliary obstruction, or in others intrahepatic cholestasis will be excluded by liver biopsy; ERCP will then be required.

Patients shown to have dilated ducts but no gallstones should have PTC performed to define accurately the level and cause of obstruction. In this group of patients ERCP may also be required. The particular value of ERCP is threefold: to exclude periampullary carcinoma, to demonstrate the anatomy of the lower end of a common bile duct not outlined by PTC and to permit collection of bile or pancreatic juice for cytology to distinguish the mass of chronic pancreatitis from that of pancreatic carcinoma and the benign bile duct stricture from carcinoma.

Recently when ultrasound has shown dilatation of the entire biliary tree with no gallstones and evident obstruction in the head of the pancreas, we have confined further investigation to duodenoscopic collection of fluid for cytology. With positive cytology for carcinoma we have then proceeded directly to surgery.

On the basis of our experience in the investigation of post-cholecystectomy problems, ultrasound and PTC have been used initially, but we often then proceed to ERCP, since at least 1 in every 3 patients presenting with jaundice after cholecystectomy has some abnormality in the duodenum as a contributory factor (Blumgart et al., 1977; Hunt and Blumgart, 1979).

Acknowledgements

We wish to thank the secretarial staff of the Department of Radiology without whose help this study would not have been possible. In particular, the help of Miss Wallace was invaluable.

References

BLUMGART L. H. (1978) Biliary tract obstruction—new approaches to old problems. *Am. J. Surg.* **135**, 19–31.

BLUMGART L. H., CARACHIE R., IMRIE C. W. et al. (1977) Diagnosis and management of post-cholecystectomy symptoms: the place of endoscopy and retrograde choledochopancreatography. *Br. J. Surg.* **64**, 509–816.

ELIAS E. (1976) Cholangiography in the jaundiced patient. *Gut* **17**, 801–811.

HUNT D. R. and BLUMGART L. H. (1979) Iatrogenic choledochoduodenal fistula: an unrecognised cause of post-cholecystectomy symptoms. (In preparation.)

LEES W. R., VALLON A. G., DENYER M. E. et al. (1978) Prospective study of pancreatic ultrasonography. Presented to the British Society of Gastroenterology, Warwick, 1978. *Gut* **19**, A449.

MCCUTCHEON A. D. (1968) A fresh approach to the pathogenesis of pancreatitis. *Gut* **9**, 296–310.

MCKAY A. J., DUNCAN J. G., IMRIE C. W. et al. (1977) Grey scale ultrasonography in acute pancreatitis: a prospective study. *Irish J. Med. Sci.* **146**, Suppl. 1, p. 26.

MCKAY A. J., DUNCAN J. G., IMRIE C. W. et al. (1978) A prospective study of the clinical value and accuracy of grey scale ultrasound in detecting gall stones. *Br. J. Surg.* **65**, 330–333.

NEIMAN H. L. and MINTZER R. A. (1977) Accuracy of biliary duct ultrasound: comparison with cholangiography. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **129**, 979–982.

STERN R. B., KNILL JONES R. P. and WILLIAMS R. (1973) Pitfalls in the diagnosis of jaundice due to carcinoma of the pancreas or biliary tree. *Br. Med. J.* **1**, 530–533.

TAYLOR K. J. W. and CARPENTER D. A. (1974a) Grey scale ultrasonography in the investigation of obstructive jaundice. *Lancet* **2**, 586–587.

TAYLOR K. J. W., CARPENTER D. A. and MCCREADY V. R. (1974b) Ultrasound and scintigraphy in the differential diagnosis of obstructive jaundice. *J. Clin. Ultrasound* **2**, 105–116.

TAYLOR K. J. W. and ROSENFIELD A. T. (1977) Grey scale ultrasonography in the differential diagnosis of jaundice. *Arch. Surg.* **112**, 820–825.

VALLON A. G., LEES W. R. and COTTON P. B. (1978) Grey scale ultrasonography in cholestatic jaundice. Presented to the British Society of Gastroenterology, Warwick, 1978. *Gut* **19**, A447.

VICARY F. R., CUSICK G., SHIRLEY I. et al. (1977) Ultrasound and jaundice. *Gut* **18**, 161–164.

Paper accepted 3 August 1978.

Br. J. Surg. Vol. 66 (1979) 166–168

The ultrasonic demonstr i portacaval shunts

L. A. BERGER, G. SAGOR AND PH ORGE*

SUMMARY

This study explores the use of ultrasound in th ment of patients with portacaval anast patients were studied; in 8 of these the anastomosis was well demonstrated. It is hat ultrasound should be the initial investigation to determine the patency of a shunt.

SINCE 1945 when portal–systemic shunting became a routine procedure in the management of bleeding varices over 100 000 shunts have been constructed (Bengmark, 1975). The most widely used anastomosis is the end-to-side portacaval shunt. This has the lowest incidence of occlusion because the stoma is large and all the portal blood flows through it (Dawson, 1977).

However, thrombosis can occur. In a patient who has a portacaval shunt and is bleeding from the upper gastrointestinal tract, knowledge of the patency, or otherwise, of the shunt would help management. Of the many tests available to determine shunt patency, the most reliable all involve invasive radiological procedures (Castell and Conn, 1972).

This study was conducted to see if ultrasound might offer a simple, accurate, non-invasive screening test of portacaval shunt patency.

Patients and methods

Ten consecutive patients with an end-to-side portacaval shunt were scanned. Eight patients had had their shunt constructed in the past while 2 were scanned in the first 2 postoperative weeks. One patient was known to have shunt dysfunction and had re-bled on many occasions following surgery; in the others the shunts were presumed patent on clinical grounds.

Using a Diasonograph 4102B with grey-scale attachment a series of longitudinal scans was performed in order to define the inferior vena cava and the portal vein. If the shunt was seen its surface position was marked with a grease pencil. If not, the line of the inferior vena cava and the portal vein was marked. Transverse scans were then performed at the level of the shunt or at the conjunction of the line of the inferior vena cava and of the portal vein.

When bowel gas prevented adequate visualization of the veins, the patient was turned into the left lateral decubitus position and scanned in both longitudinal and transverse planes.

Results

The portacaval shunt was shown in longitudinal section in only 2 patients. In one of these the inferior vena cava doubled in size at the site of the shunt, a reflection of high portal blood flow (*Fig.* 1). Surprisingly, in the other patient there was no change in calibre of the inferior vena cava, yet this patient had the largest anastomosis on ultrasound examination. In these 2 patients and in 3 others the shunt was well seen in transverse section (*Fig.* 2). In 1 patient the splenic vein, portal vein and inferior vena cava could be seen as a continuous arc.

Gas precluded adequate examination in 5 patients; however, after the patients had been turned into the left lateral decubitus position, the shunt was well seen in transverse section in 3.

The shape of the shunt generally resembled a dumbbell and adjacent to the stoma well-defined high level echoes were usually seen, probably due to fibrous tissue. In patients without portacaval shunts the portal vein can also be seen just anterior to the inferior vena cava, but in every case the two veins are separate and their walls can be seen to be intact.

In the patient presumed to have had shunt dysfunction, a stenotic connection between the inferior vena cava and the portal vein was clearly shown (*Fig.* 3).

Thus, in 8 out of 10 patients the status of the anastomosis was well demonstrated.

Discussion

After an end-to-side portacaval anastomosis some 12 per cent of patients will, at some time, bleed from the upper gastrointestinal tract (Reynolds et al., 1966; Foster et al., 1971; Jackson et al., 1971; Zeegan et al., 1973; Resnick et al., 1974; Bengmark, 1975). Forty per cent of these haemorrhages will be due to varices. This accords well with the 5 per cent incidence of thrombosis of end-to-side portacaval shunts (Voorhees et al., 1970; Foster et al., 1971; Jackson et al., 1971; Resnick et al., 1974).

Demonstrating that varices are present is not sufficient to conclude that they are the source of bleeding. Following a successful shunt varices will persist in 40–70 per cent of patients gradually reducing in size over several years (Ellis et al., 1956; Reynolds et al., 1966; Jackson et al., 1971). Bleeding from varices can occur with a patent shunt (Resnick et al., 1974), but this is uncommon. The demonstration of shunt patency would therefore suggest an alternative site for bleeding.

The effect of an end-to-side anastomosis on ascites is variable. Some patients become free of ascites, others more easily controlled and still others show little or no improvement (Rousselot et al., 1963). Nevertheless, the sudden deterioration of a previously stable situation can be due to shunt thrombosis.

We believe that scanning in the left lateral decubitus position will improve the rate of demonstration of portacaval shunts. In this position both the portal and systemic veins dilate and are more easily seen; colonic gas rises into the ascending colon away from the field of interest and the liver descends, thus becoming an ultrasonic window.

The 2 patients examined in the immediate postoperative period found scanning near their wound painful. Excessive bowel gas requiring the use of the lateral decubitus position added to their discomfort. How useful ultrasound examination will prove to be in a patient bleeding soon after operation has yet to be shown. Real-time scanners, which are less unpleasant for an ill patient, or scanning from the side, away from the wound, may be better alternatives. It is in the immediate postoperative period, when shunt thrombosis accounts for 20–25 per cent of deaths

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* Departments of Radiology and Surgery, The Royal Free Hospital, London.

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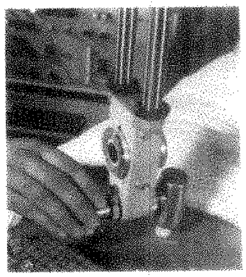

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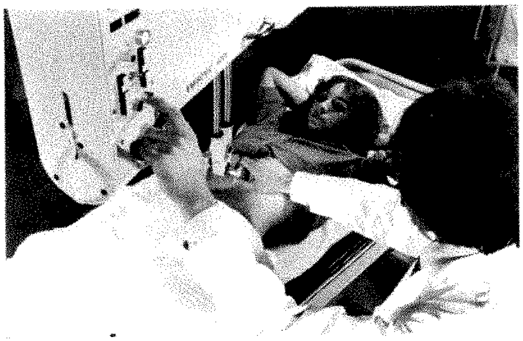

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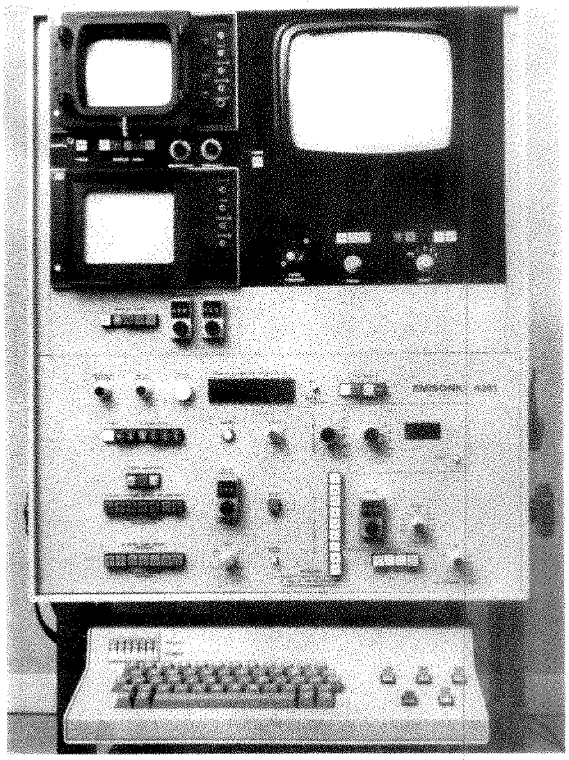

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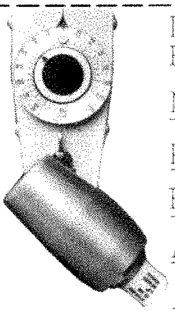

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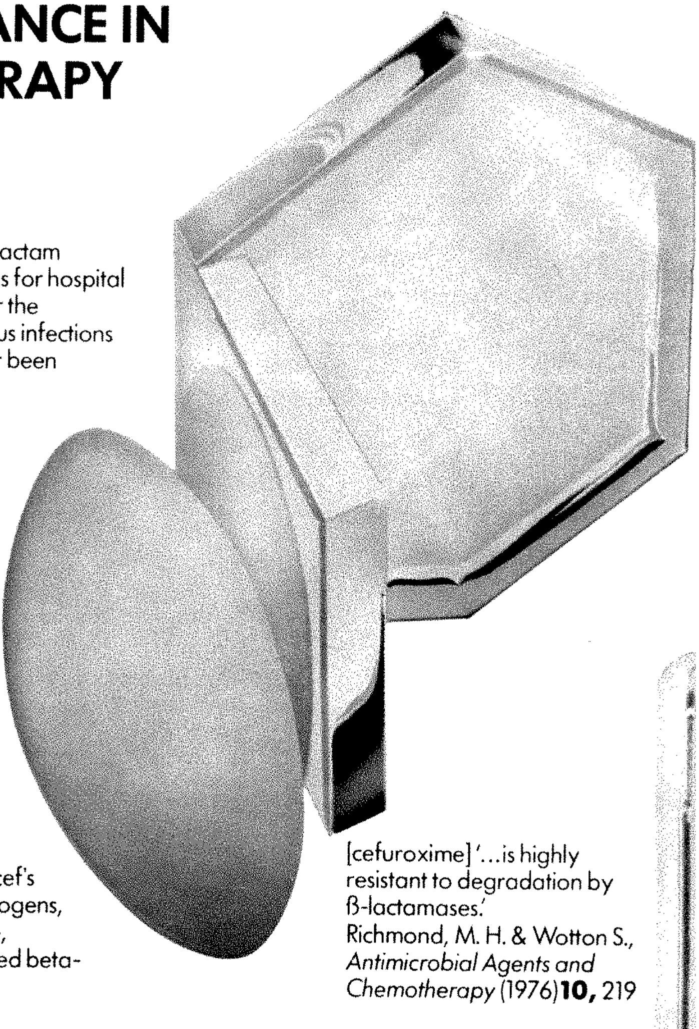

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Richmond, M. H. & Wotton S., *Antimicrobial Agents and Chemotherapy* (1976) **10,** 219

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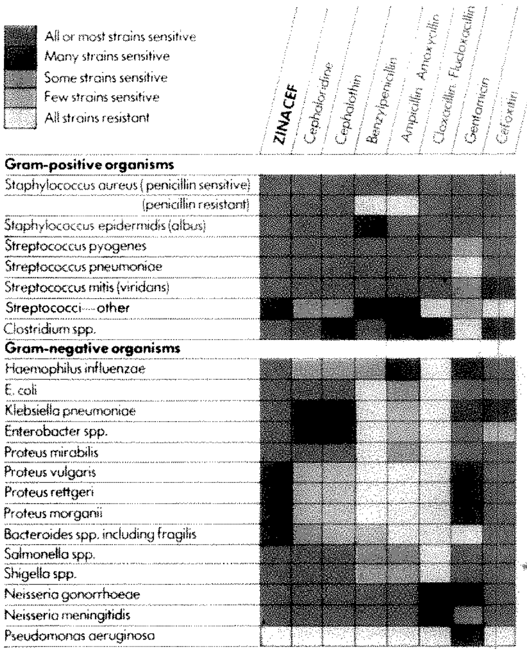

▓ All or most strains sensitive
■ Many strains sensitive
▒ Some strains sensitive
░ Few strains sensitive
□ All strains resistant

	ZINACEF	Cephaloridine	Cephalothin	Benzylpenicillin	Ampicillin Amoxycillin	Cloxacillin Flucloxacillin	Gentamicin	Cefoxitin
Gram-positive organisms								
Staphylococcus aureus (penicillin sensitive)	▓	▓	▓	▓	▓	▓	▓	▓
(penicillin resistant)	▓	▓	▓	□	□	▓	▓	▓
Staphylococcus epidermidis (albus)	▓	▓	▓	■	▓	▓	▓	▓
Streptococcus pyogenes	▓	▓	▓	▓	▓	▓	▒	▓
Streptococcus pneumoniae	▓	▓	▓	▓	▓	▓	░	▓
Streptococcus mitis (viridans)	▓	▓	▓	▓	▓	▓	▒	■
Streptococci—other	■	▒	▒	■	■	░	▒	░
Clostridium spp.	▓	▓	■	▓	■	■	░	■
Gram-negative organisms								
Haemophilus influenzae	▓	▒	▒	▒	■	□	■	▓
E. coli	▓	▓	▓	□	▒	□	▓	▓
Klebsiella pneumoniae	▓	■	■	□	░	□	■	■
Enterobacter spp.	▓	■	■	□	░	□	▓	░
Proteus mirabilis	▓	▓	▓	□	▒	□	▓	▓
Proteus vulgaris	■	░	░	□	□	□	■	▓
Proteus rettgeri	■	░	░	□	□	□	■	▓
Proteus morganii	■	░	░	□	□	□	■	▓
Bacteroides spp. including fragilis	■	▒	▒	░	□	□	□	▓
Salmonella spp.	▓	▓	▓	▒	▒	□	▓	▓
Shigella spp.	▓	▓	▓	▒	▒	□	▓	▓
Neisseria gonorrhoeae	▓	▓	▓	▓	▓	■	■	▓
Neisseria meningitidis	▓	▓	▓	▓	▓	■	▒	▓
Pseudomonas aeruginosa	□	□	□	□	□	□	■	□

ZINACEF

Prescribing information

Presentation
Vials of 250mg, 750mg and 1·5 gram and infusion pack of 1·5 gram. All containing cefuroxime as cefuroxime sodium.

Indications
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Gonorrhoea

Dosage
Adults: Generally 750mg t.d.s. i.m. or i.v. Severe infections 1·5 gram t.d.s. i.v. Frequency of injections can be increased to six-hourly if necessary.
Infants and children: 30 to 100mg/kg/day in three or four divided doses. 60mg/kg/day will be appropriate for most infections.
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Gonorrhoea: Single dose of 1·5 gram (2 x 750mg i.m. into different sites).

Contra-indications
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Precautions
Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins.
As with all drugs, Zinacef should be administered with caution during the early months of pregnancy.
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Adverse reactions are rare and generally mild and transient, e.g., rashes, gastro-intestinal disturbance, candida intertrigo, decreased haemoglobin concentration, eosinophilia, a positive Coombs' test, transient rises in serum liver enzymes and transient pain (after i.m. injection).

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Trasylol may in very rare cases (less than 0.1%) cause hypersensitivity reactions.

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Ampoules of 100,000 KIU (Kallikrein Inactivator Units)
Ampoules of 200,000 KIU*
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PL0010/5900

1) Schneider et al., Chirurg **47,** 185 (1976)
2) McMichan et al., Med. Welt **27,** 2331 (1976)

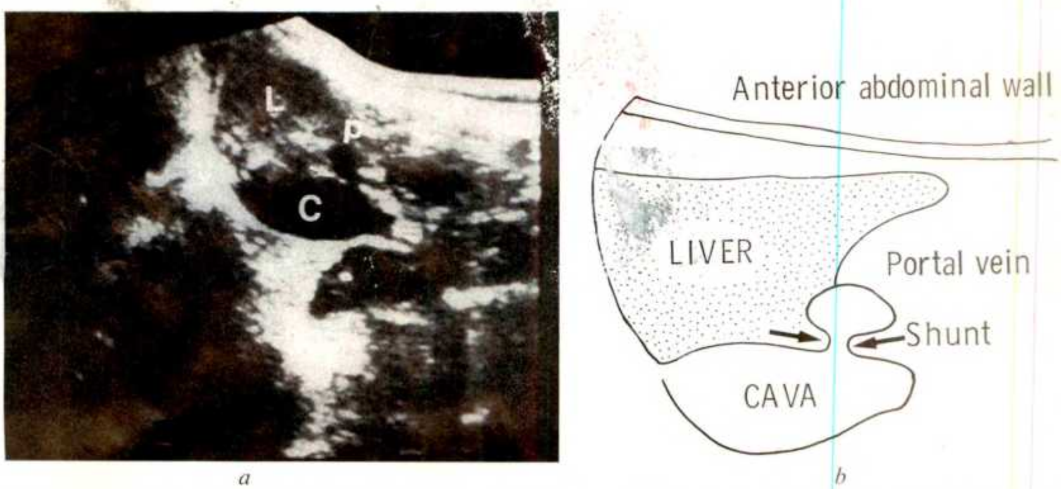

Fig. 1. The portacaval shunt shown in longitudinal section: note the increase in the diameter of the inferior vena cava distal to the shunt, indicating the high flow across the shunt. L, liver; P, portal vein; C, vena cava; the arrow points to the shunt.

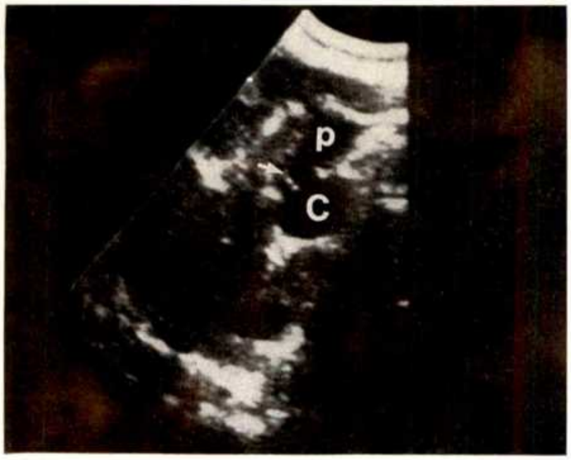

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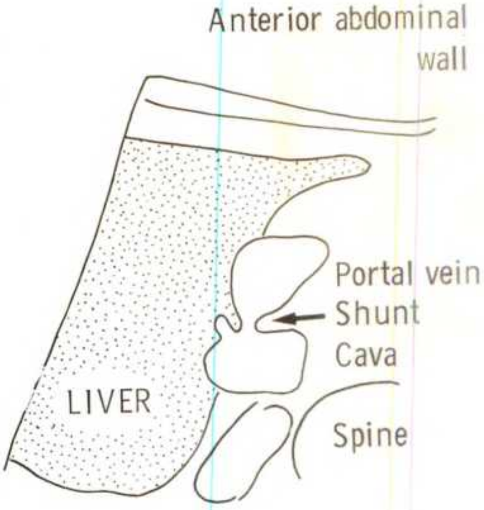
Fig. 2. The same shunt seen in transverse section: note that the true diameter of this shunt is best seen in this plane. P, portal vein; C, vena cava; the arrow points to the shunt.



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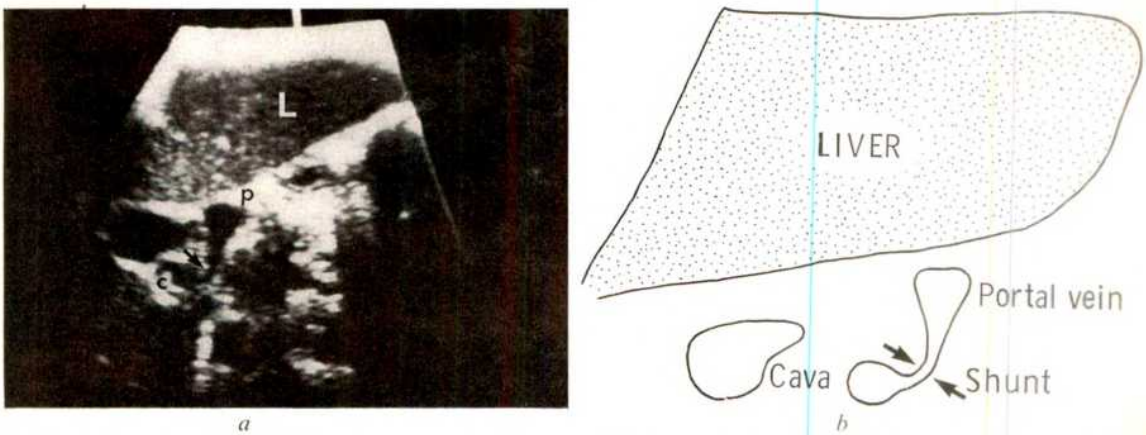

Fig. 3. In this patient there was shunt dysfunction. An irregular stenotic anastomosis can be seen. L, liver; P, portal vein; C, vena cava; the arrow points to the shunt.

(Hellstrom and Jackson, 1970; Foster et al., 1971), that ultrasound could play its most important role.

Conclusion

This report and a previous smaller series (Goldberg and Patel, 1977) have shown that ultrasound can demonstrate end-to-side portacaval anastomoses clearly in most patients. We, therefore, suggest that it should be the initial investigation for shunt patency. Angiography would then be reserved for those patients in whom ultrasound had failed to demonstrate the shunt or for confirmation that a shunt had thrombosed.

Addendum

Since we submitted this paper the patient with the stenotic shunt has undergone a successful mesocaval shunt. Two further patients have had their portacaval shunts clearly demonstrated: one was widely patent and the other markedly stenotic. The latter patient was bleeding from varices.

Acknowledgement

The authors wish to thank Miss K. Breen for her secretarial assistance.

References

BENGMARK S. (1975) Surgical management of portal hypertension. *Clin. Gastroenterol.* **5**, 395–423.

CASTELL D. O. and CONN H. O. (1972) The determination of porta-caval shunt patency: a critical review of methodology. *Medicine* **51**, 315–336.

DAWSON J. L. (1977) Portal hypertension. In: TAYLOR S. (ed.) *Recent Advances in Surgery*, 9. Edinburgh, Churchill Livingstone, pp. 55–82.

ELLIS D. S., LINTON R. R. and [illegible]ONES C. M. (1956) Effect of venous-shunt surgery on live[illegible] function in patients with portal hypertension. A follow-up study of 125 patients operated on in the last 10 years. *N. Engl. J. Med.* **254**, 931–936.

FOSTER J. H., ELLISION [illegible] DONOVAN T. J. et al. (1971) Quantity and quality of surviv[illegible]fter portosystem[illegible]nts. *Am. J. Surg.* **121**, 490–500.

GOLDBERG B. B. and [illegible]ATEL [illegible] (19[illegible] porta-caval shun[illegible] *J. Cli*[illegible]

HELLSTROM H. R. and JACK[illegible] of porta-caval anasto[illegible] 201–205.

JACKSON F. C., PERRIN E. B., FELIX [illegible] clinical investigation of the porta-ca[illegible] Survival analysis of the therapeutic operation. [illegible] *Surg.* **174**, 672–698.

RESNICK R. H., IBER F. L., ISHIHARA A. M. et al. (1974) A controlled study of the therapeutic porta-caval shunt. *Gastroenterology* **67**, 843–857.

REYNOLDS T. B., HUDSON N. M., MIKKELSEN M. C. et al. (1966) Clinical comparison of end-to-side and side-to-side portacaval shunt. *N. Engl. J. Med.* **274**, 706–710.

ROUSSELOT L. M., PANKE W. F., BONO R. F. et al. (1963) Experiences with porta-caval anastomosis. Analysis of 104 elective end-to-side shunts for the prevention of recurrent hemorrhage from oesophagogastric varices (1952–1961). *Am. J. Med.* **34**, 297–307.

VOORHEES A. B., PRICE J. B. and BRITTON R. C. (1970) Portosystemic shunting procedures for portal hypertension. Twenty-six year experience in adults with cirrhosis of the liver. *Am. J. Surg.* **119**, 501–505.

ZEEGAN R., STANSFELD A. G., DAWSON A. M. et al. (1973) Portal decompression for intrahepatic portal hypertension: long-term follow-up of 253 cases. *Gut* **14**, 816.

Paper accepted 11 September 1978.

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Grey-scale ultrasonography and endoscopic pancreatography after pancreatic trauma

A. G. VALLON, W. R. LEES AND P. B. COTTON*

SUMMARY

We have recently used grey-scale ultrasonography and endoscopic pancreatography to investigate 11 patients with symptoms attributed to pancreatic trauma weeks, months or even years earlier. The pancreas was normal in one patient, and another, who presented with pain and jaundice after a car accident, was shown to have cancer of the pancreatic head. The remaining patients all had local lesions due to trauma; ultrasound showed a mass or cyst close to the point of duct obstruction or stenosis shown on pancreatography. Ultrasonography and pancreatography can together provide a precise map with which to plan effective management in patients having suffered pancreatic trauma.

THE pancreas is vulnerable to an external crushing injury such as may occur in a road traffic accident. Severe pain usually develops within hours and frequently leads to emergency laparotomy, at which damage to other organs may well be apparent. Specialist imaging investigations have little place in this context. However, we have recently seen 11 patients some time after the initial accident in whom persisting symptoms have been attributed to the injury. Grey-scale ultrasonography and endoscopic pancreatography have provided valuable information in the management of these patients.

Patients and methods

There were 8 men and 3 women, with an age range of 13–58 years (*Table I*). All except 3 patients were investigated within 6 months of injury and had been unwell throughout that period. Two patients had been having intermittent symptoms for 6 and 15 years following injury. Five patients had been involved in road traffic accidents; 4 others had been injured during sporting activities, in all 4 the injury had seemed trivial at the time and 2 players had been able to complete the game in which they had been playing. One patient had been assaulted and another claimed to have developed pancreatic-type pain after having been blown across a street by a bomb in Vietnam. Eight of the patients had undergone at least one surgical procedure before our investigations (*Table I*).

Grey-scale ultrasonography was performed using a modified Nuclear Enterprises Diasonograph NE 4102 with NE 4104 grey-scale facility. Gastroduodenoscopy and cholangiopancreatography were performed in the standard manner under mild sedation (Cotton, 1977).

Results

Ultrasonography was performed in 9 patients (*Table I*). No useful information was obtained in *Case* 3 who was examined shortly after surgery. In *Case* 10 a normal pancreas was correctly demonstrated. The other 7 scans showed pancreatic abnormalities which were localized in 6; 2 of these mass lesions were reported as cystic (*Table I*) (*Fig.* 1). Ultrasonography suggested multiple abdominal abscesses in *Case* 7; she required further urgent laparotomy and drainage of the abscesses. A pancreatic transection was demonstrated and a left hemipancreatectomy proved curative.

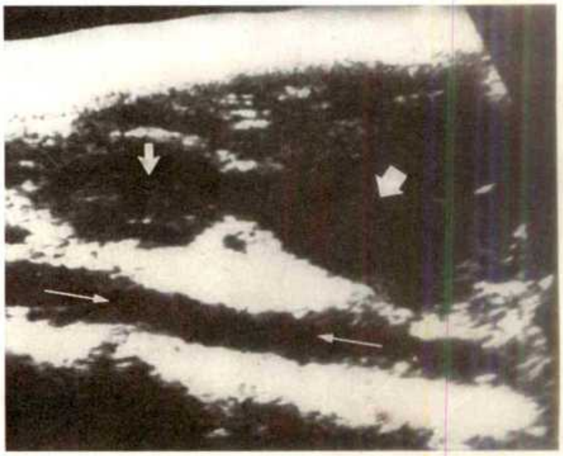

Fig. 1. (*Case* 4.) Longitudinal ultrasound scan showing the aorta posteriorly (long arrows), a section through the pancreatic body (small arrow on left) and a pseudocyst extending from the pancreas into the lesser sac (large arrow on right).

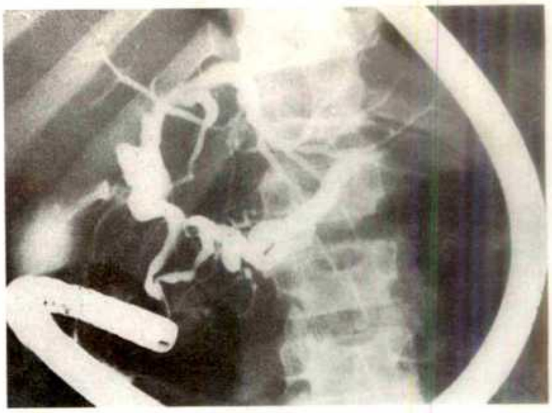

Fig. 2. (*Case* 8.) Mass lesion in the pancreatic head with upstream dilatation of the biliary system and pancreatic duct.

Endoscopic pancreatography was normal in one patient (*Case* 10), as was the ultrasound scan; it eventually became abundantly clear that this patient suffered from Munchausen's syndrome. A major duct lesion was shown in the other 9 patients (*Table I*). In *Case* 9, who had developed pain 3 days after a road traffic accident and who eventually became jaundiced, ERCP showed a stricture of the lower bile duct diagnostic of carcinoma; the history of trauma had been irrelevant. In *Case* 8, a boy of 12, ERCP showed narrowing of the common bile duct and the pancreatic duct within the head of the pancreas, and

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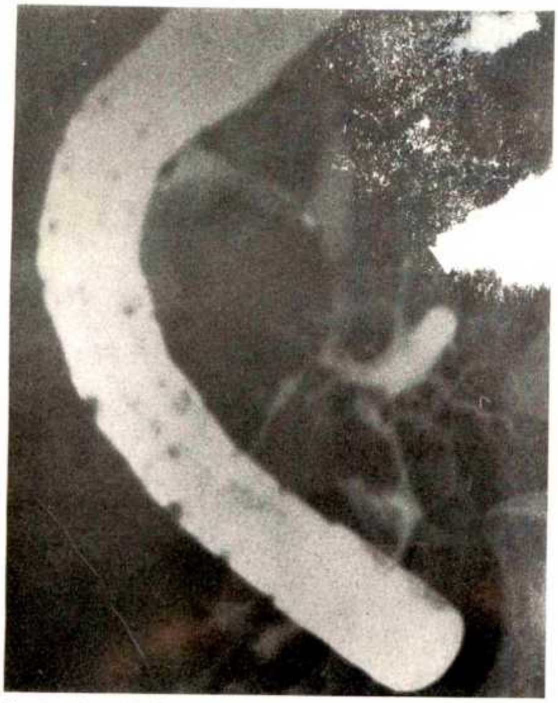

Fig. 3. (*Case* 1.) Complete pancreatic duct obstruction (arrowed) close to the papilla.

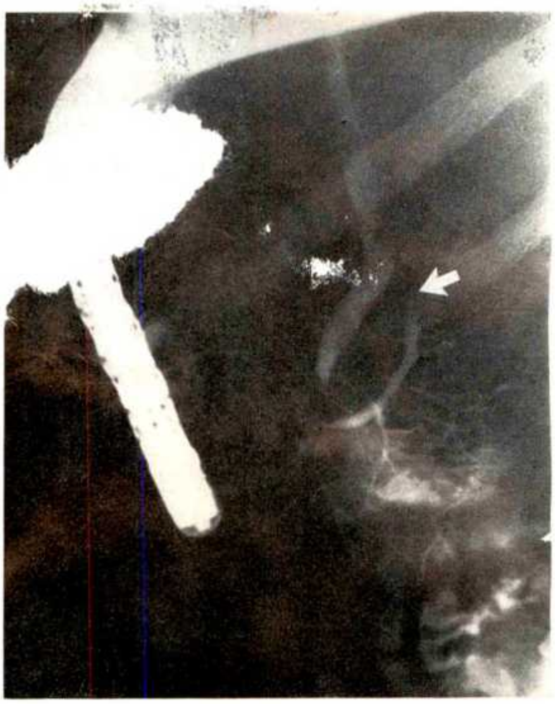

Fig. 5. (*Case* 4.) Complete obstruction of the main duct (arrowed) near the neck of the pancreas.

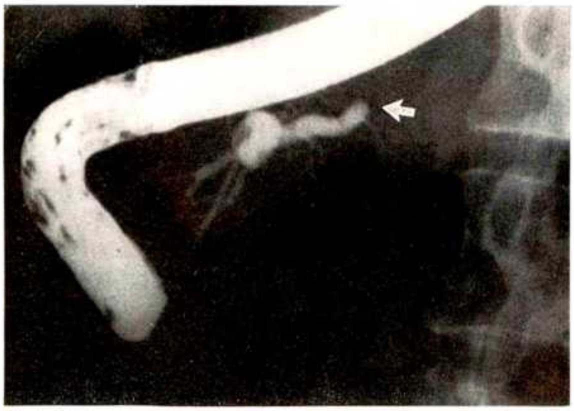

Fig. 4. (*Case* 2.) Complete obstruction in the neck of the gland (arrowed).

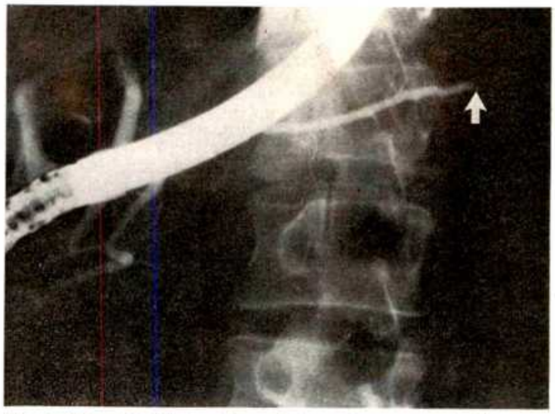

Fig. 6. (*Case* 6.) Obstruction of the main pancreatic duct close to the tail (arrowed).

upstream dilatation (*Fig.* 2). The appearances suggested a mass lesion in the head of the pancreas, which was found at surgery to be a pseudo-aneurysm resulting from erosion of the pancreaticoduodenal artery, presumably within an inflammatory mass. This patient did well after pancreaticoduodenectomy. The remaining 6 patients submitted to ERCP were all shown to have an obstruction of the main duct; the position varied considerably (*Figs.* 3–6). These abnormalities were all confirmed at surgery; in one patient (*Case* 3) the extent of the injury and adhesions from previous surgery made definitive resection impossible. One patient (*Case* 4) simply underwent pseudocyst gastrostomy with considerable short term improvement. The remaining patients have had excellent results from left hemipancreatectomy (*Table I*).

In the 8 patients who underwent both ultrasonography and ERCP, results agreed and complemented each other. The mass seen on scanning corresponded to the site of the main duct abnormality in 4 out of 5 patients.

The final patient (*Case* 5) had additional interest. He first presented with acute pancreatitis 96 h after sustaining an injury on the rugby field. Symptoms recurred following pseudocyst gastrostomy; complete pancreatic transection was recognized at a second operation and left hemipancreatectomy was performed. Despite this he continued to have repeated

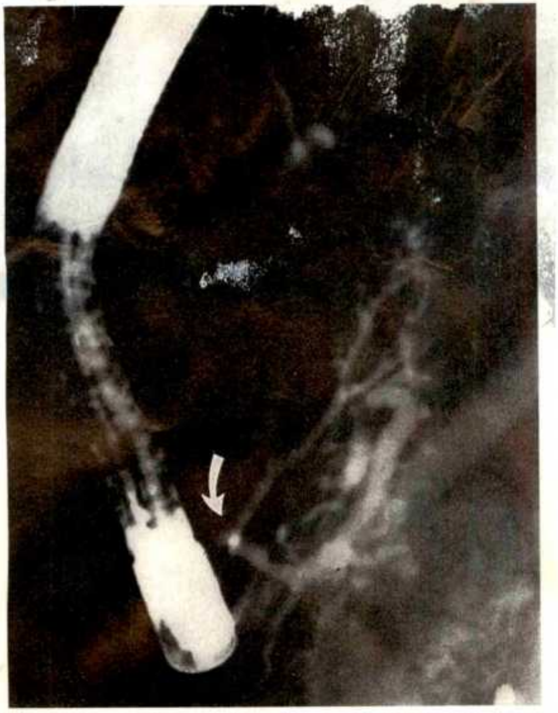

Fig. 7. (*Case* 5.) Cannulation of the accessory papilla (arrowed) and injection of contrast through Santorini's duct outlining the head of the pancreas up to the point of previous surgical resection. The ducts are abnormal, indicating chronic pancreatitis.

attacks of pancreatitis over the next 6 years. At ERCP cannulation of the main papilla revealed only the biliary system; however, cannulation of the accessory papilla and Santorini's duct outlined an abnormal head of pancreas to the point of surgical resection (*Fig*. 7). He has been pain-free following subtotal (95 per cent) pancreatectomy, but has both endocrine and exocrine insufficiency. In this patient the congenital duct anomaly (separate ventral and dorsal elements to the pancreas) probably contributed to the development and persistence of pancreatitis after the original injury.

In no case was the result of ultrasound or pancreatography misleading.

Discussion

Trauma to the pancreas is relatively uncommon, and few clinicians have wide experience in its treatment. The high initial mortality of around 20 per cent (Editorial, 1975) is rarely due to damage to the pancreas itself but to associated injuries or haemorrhage from adjacent major vessels. Steele et al. (1973) reported their experience with 85 cases of pancreatic trauma. Surgical management consisted of drainage alone for laceration and contusion that did not involve major ductal structures and segmental pancreatectomy for those that did. However, most authors state that assessment of the pancreas at operation may be difficult, and significant pancreatic injuries, including complete transections, have been missed at laparotomy (Northrup and Simmons, 1972), as in 6 of our patients. In all our patients with pseudocysts,

Table I: CLINICAL DATA AND RESULTS OF INVESTIGATIONS IN 11 PATIENTS WITH A HISTORY OF PANCREATIC TRAUMA

Patient	Age (yr)/Sex	Injury	Onset	Early surgery	Interval to study	US	ERP	Surgical findings and procedure	Outcome	Follow-up
1	36 M	Car	Immediate	External drainage of pseudocyst	6 wk	Head mass 6 × 6 cm	Head block	Pseudocyst: transection, left hemipancreatectomy	[illegible]ent	3 [illegible]
2	30 F	Car	2 hr	—	4 wk	Head cyst 3 × 4 cm	Neck block	Pseudocyst: transection, left hemipancreatectomy	Excellent	3 yr
3	18 M	M/cycle	Immediate	Cyst gastrostomy, fistula	6 wk	Poor views	Midbody block	Multiple trauma and adhesions	Died	—
4	21 M	Soccer	12 hr	Multiple drains, fistula	14 mth	Head cyst 4 × 6 cm	Head block	Cyst gastrostomy	Improved	1 yr
5	26 M	Rugby	96 h	Cyst gastrostomy, left hemipancreatectomy after 1 yr	6 yr	—	Pancreatitis, congenital anomaly	95% resection	Pain-free; insufficiencies	18 mth
6	30 M	Toboggan	36 h	Cyst gastrostomy, splenectomy	15 yr	Tail mass 3 × 3 cm	Tail block	Excision of atrophic tail	Good	2 yr
7	14 F	Surfboard	4 h	Multiple drains	2 mth	Body mass 6 × 5 cm	—	Transection: abscess drained, left hemipancreatectomy	Excellent	2 yr
8	12 M	Assault	?	Pancreatitis	6 mth	Head mass 5 × 7 cm	Head mass with dilated ducts upstream	Pseudoaneurysm: pancreaticoduodenectomy	Excellent	3 yr
9	58 F	Car	96 h	—	2 wk	—	Head cancer	Biliary bypass	Died	—
10	38 M	'Bomb'	6 h	—	6 mth	Normal	Normal	None	Munchausen syndrome	2 yr
11	19 M	Car	Immediate	Liver sutured, drains, fistula	2 wk	Tail, acute pancreatitis	Head block	Neck transection: left hemipancreatectomy	Excellent	6 wk

US, Ultrasound; ERP, pancreatography.

the ductal system was in fact disrupted and ERCP showed complete obstruction. Symptoms [illegible] slow to develop after isolated blunt pancreatic [illegible] (Blandy et al., 1959; Bracey, 1961). *Case* 5 in [illegible] series did not develop abdominal symptoms [illegible] 96 h after an injury which resulted in complete pancreatic transection. Symptoms may even be [illegible] until a pseudocyst develops weeks or [illegible] (Northrup and Simmons, 1972).

Specialist imaging investigations are unlikely to give useful clinical information in the emergency situation, although developments in ultrasound scanning may change the position. It is in patients in whom the initial injury has been insufficient to lead to early laparotomy, or where symptoms have persisted following it, that definitive investigation is important. We have found the combination of grey-scale ultrasonography and endoscopic pancreatography to provide complementary and accurate information about the pancreas (Lees et al., 1979). Pancreatography provides the essential map for any surgery which may be necessary (Cotton, 1977). Although the classic duct injury lies over the vertebral column, it is clear from this small series that the duct may become occluded at any point. Grey-scale ultrasonography should always be performed first, and this technique is particularly accurate in the diagnosis of cystic collections (Leopold, 1972; Bradley and Clements, 1974). ERCP carries a risk of introducing infection into pseudocysts; when ultrasound shows a cyst, pancreatography should be performed only as an immediate preoperative procedure.

In discussing the management of pancreatic trauma, Northrup and Simmons (1972) stress the importance [illegible] understanding the nature of the injury for formu- [illegible] surgical intervention. Preoperative [illegible] pancreatography [illegible] that this [illegible]

Refer[illegible]

BLANDY J. P., HAM[illegible] and KERR W. F. (1959) Isolated injury of the pancreas from non-penetrating abdominal trauma. *Br. J. Surg.* **47**, 150–155.

BRACY D. N. (1961) Complete rupture of the pancreas. *Br. J. Surg.* **48**, 575–576.

BRADLEY E. L. and CLEMENTS J. L. (1974) Implications of diagnostic ultrasound in the surgical management of pancreatic pseudocysts. *Am. J. Surg.* **127**, 163–173.

COTTON P. B. (1977) Progress report: ERCP. *Gut* **18**, 316–341.

EDITORIAL (1975) Blunt pancreatic injury. *Br. Med. J.* **2**, 4–5.

LEES W. R., VALLON A. G., DENYER M. E. et al. (1979) A prospective study of pancreatic ultrasonography. *Gut.* (In the press.)

LEOPOLD G. R. (1972) Pancreatic echography. A new dimension in the diagnosis of pseudocysts. *Radiology* **104**, 365–369.

NORTHRUP W. F. and SIMMONS R. L. (1972) Pancreatic trauma. A review. *Surgery* **71**, 27–43.

STEELE M., SHELDON G. F. and BLANDELL F. W. (1973) Pancreatic injuries. *Arch. Surg.* **106**, 544–549.

Paper accepted 11 September 1978.

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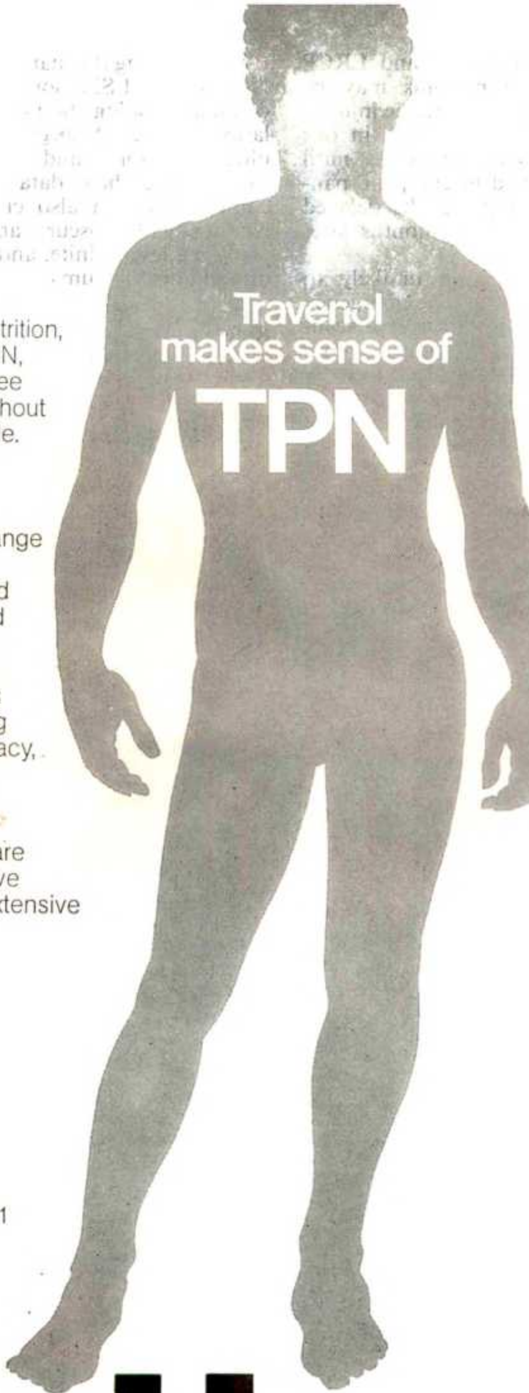

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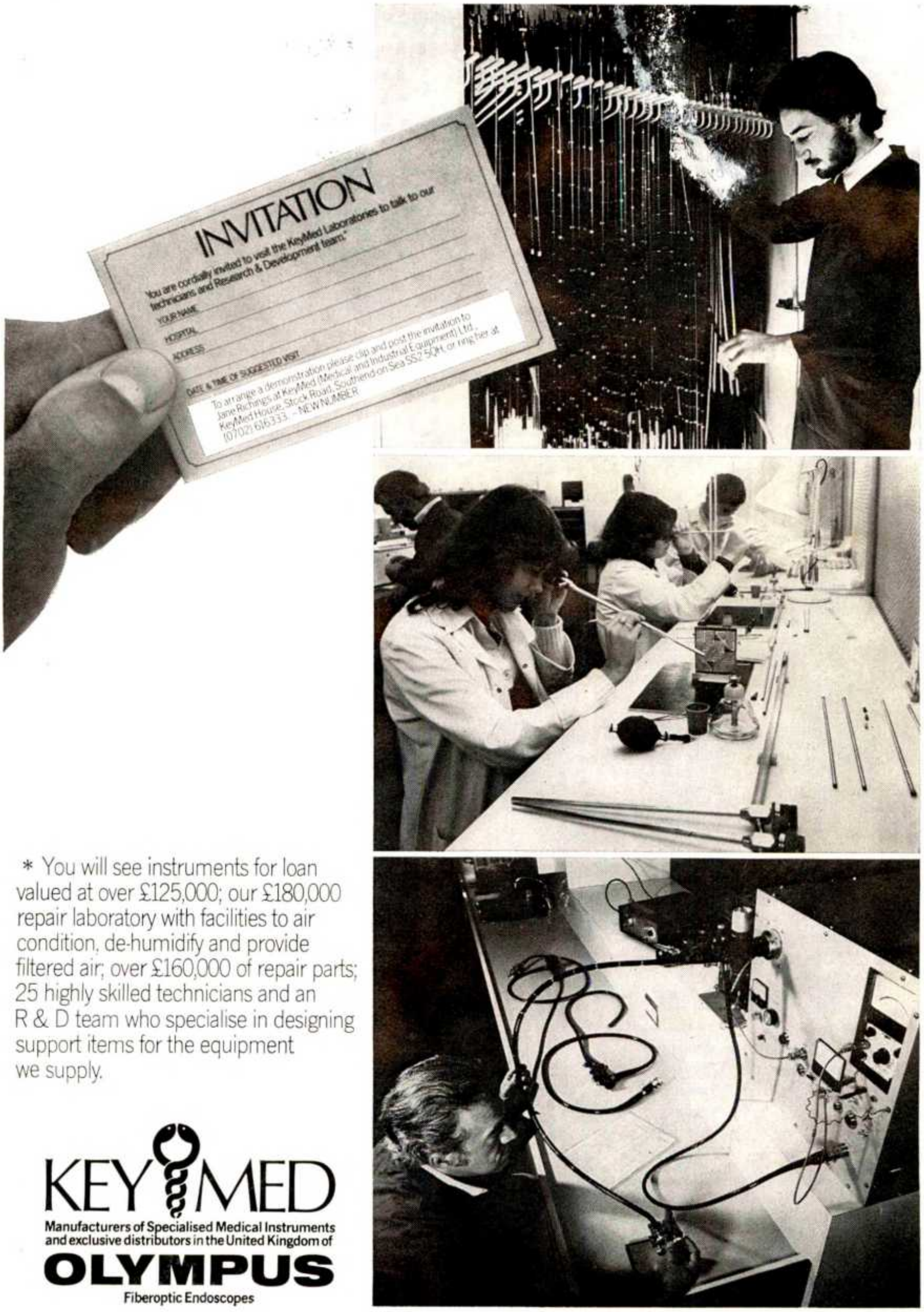

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Br. J. Surg. Vol. 66 (1979) 173–176

Infusion cholecystography in the diagnosis of acute cholecystitis

D. J. PINTO, M. BURKE, R. A. WILKINS AND A. E. KARK*

SUMMARY

The use of infusion cholecystography as an aid in the diagnosis of acute cholecystitis was investigated in 21 patients. Seventeen of 18 patients (94 per cent) with positive cholecyst-tomograms who underwent laparotomy had confirmation of acutely inflamed gallbladders both macroscopically and histologically. These findings suggest that infusion cholecystography can make a significant contribution in reducing the incidence of misdiagnosis in acute cholecystitis, and that the investigation should be part of the management of patients in whom early surgery is planned.

THE timing of operative treatment for acute cholecystitis continues to be a controversial topic. In the past, the overwhelming opinion in Britain has favoured a policy of initial conservative management followed by planned surgery in later months. Recently, the role of early surgery has been critically re-examined as operation within the first few days of hospital admission has several advantages. Provided that the operation is undertaken by an experienced surgeon, after adequate fluid replacement and cardiorespiratory and renal assessment, the morbidity and mortality are similar to those of the conservative management of acute cholecystitis (van der Linden and Sunzel, 1970; Raine and Gunn, 1975) and both diagnosis and treatment are completed during a single hospital admission with a rapid return to full activity (Editorial, 1976). However, if a policy of early surgery is to be widely adopted, accurate diagnosis is mandatory and thus a critical evaluation of clinical and investigative data is desirable.

The most widely used diagnostic radiographic test in acute cholecystitis is intravenous cholangiography (Thorpe et al., 1973) but its reliability has been questioned (Eckelberg et al., 1970; Mujahed et al., 1974) and there is a mortality of 1 : 5000 (Love, 1976). Oral cholecystography is time-consuming (12–16 h), may require repetition and the contrast medium may not be absorbed from the gastrointestinal tract.

The non-invasive technique of ultrasonography is useful in delineating gallbladder size and wall thickness, and the presence of calculi. However, ultrasonography is not widely available and the results obtained are closely dependent on interpretation. In addition, the presence of gas in the alimentary tract adjacent to the gallbladder prevents ultrasonic demonstration of this organ in about 20 per cent of patients (Meire, 1978).

Because of the limitations of current methods of diagnosis of acute cholecystitis the radiographic technique described by Love (1976) merits further investigation. The technique consists of rapid visualization of the inflamed gallbladder by infusion cholecystography using Urografin. Love (1976) showed a 96 per cent correlation between a positive infusion tomogram of the gallbladder and histological evidence of acute inflammation. The method is particularly suited to an emergency situation as it requires no special preparation and only takes about 40 min to perform.

We report a pilot study where infusion cholecystography was used as a diagnostic aid in patients undergoing planned early cholecystectomy for acute cholecystitis, and where the radiological, operative and histopathological findings were compared in each case.

Patients and methods

Twenty-one consecutive patients who were admitted to one surgical firm with a clinical diagnosis of acute cholecystitis were studied. The average age was 60·3 years (range 46–76) and 52 per cent of the patients were women. All the patients presented with pain in the right hypochondrium with or without a history of nausea and vomiting. Localized peritonism was found on palpation. Leucocytosis and pyrexia were present in all cases. Nasogastric suction, intravenous fluid replacement and regular analgesia were instituted on admission.

Technique

An initial scout film of the right upper quadrant of the abdomen was taken, 300 ml of 30 per cent methylglucamine diatrizoate (Urografin) was infused intravenously over a period of 15–20 min. Anteroposterior tomographic cuts of the gallbladder area were then made, starting at a level one-third of the distance from the anterior abdominal wall to the top of the table and proceeding forward at 1 cm intervals for 4–5 cm. The tomographic cuts were immediately reviewed by the radiologist and further radiographs obtained if necessary.

Results

Eighteen of the 21 patients had a positive infusion tomogram of the gallbladder and underwent early operation. Seventeen of these tomograms clearly demonstrated a curvilinear opacity, about 3–5 mm thick, delineating the contour of the gallbladder (*Fig.* 1) and one showed diffuse opacification only in the gallbladder area. One of the positive tomograms also showed that the fundus of the gallbladder was grossly thickened (*Fig.* 2). This increased thickness was contiguous to the curvilinear opacity, suggesting an intramural lesion rather than an intraluminal opacity. The scout film did not reveal an opaque stone and a tentative radiological diagnosis of carcinoma of the gallbladder in an inflamed organ was made.

Seventeen of the 18 patients with positive infusion tomograms were found to have acutely inflamed gallbladders at laparotomy. Four had macroscopic evidence of focal necrosis especially in the fundus and of these one had a pericholecystic abscess. The eighteenth patient had a normal gallbladder but was found to have a sealed-off perforation of a duodenal ulcer in the anterosuperior aspect of the first part of the duodenum. There was considerable periduodenal oedema with adhesions between the gallbladder, duodenum and hepatic flexure of the colon. In this patient the tomogram showed diffuse opacification in

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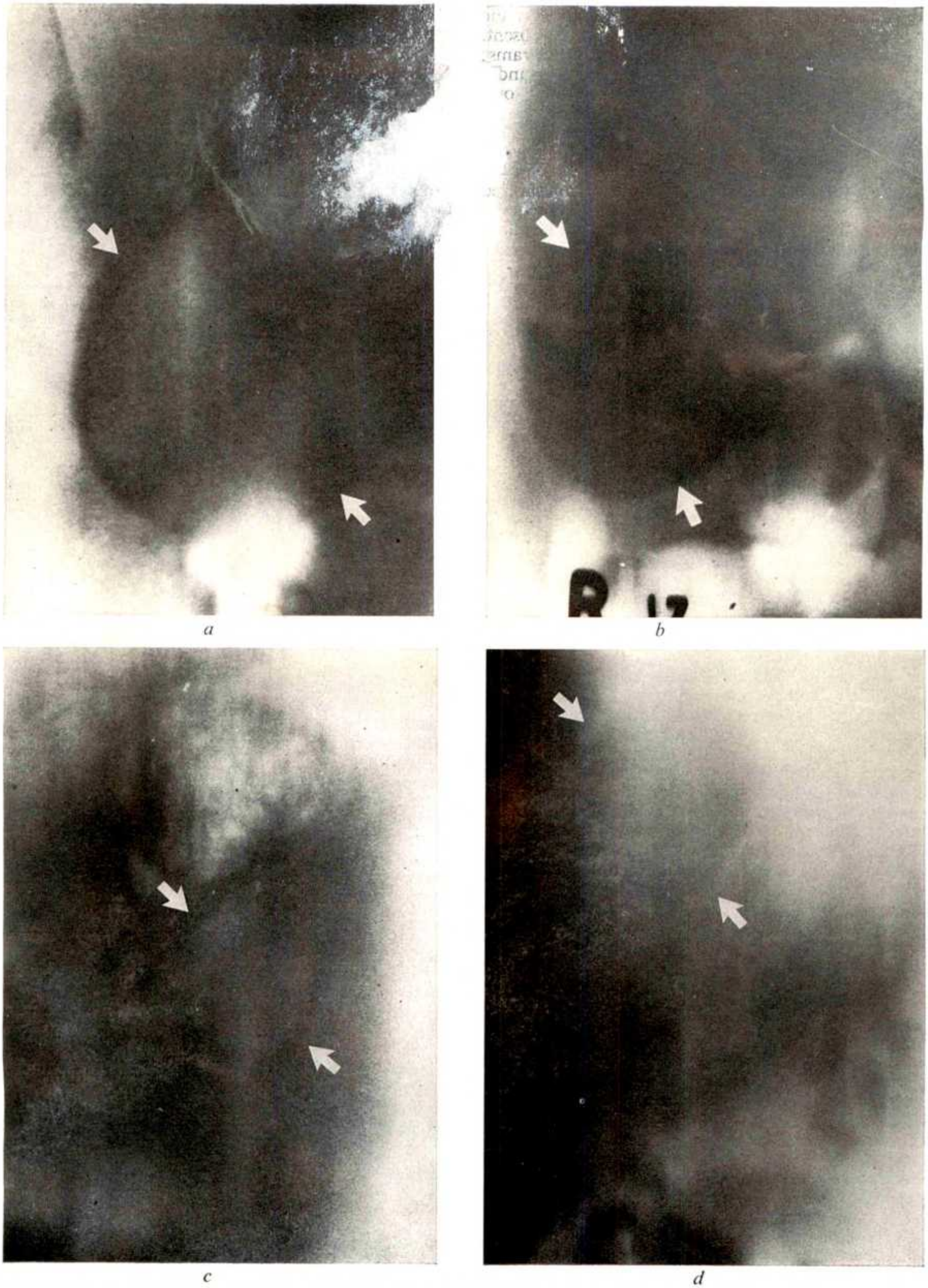

Fig. 1. White arrows demonstrate a translucent area surrounded by a curvilinear opacity a few millimetres thick, i.e. the gallbladder wall.

the gallbladder but the cur the hallmark of an inflamed gal Three patients had negative in they were treated conservatively and be weeks later were investigated by means cholecystogram and barium meal. In one, cholecystogram and barium meal were norm second had a normal cholecystogram but the ba meal showed a duodenal ulcer. The third patient h a normal barium meal but the cholecystogram showe stones in the gallbladder. However, at subsequent cholecystectomy 4 weeks after initial hospitalization, there was no macroscopic or histological evidence of recent inflammation. Thus, in 2 of the 3 patients with negative infusion tomograms there was no subsequent evidence of gallbladder pathology and, although gallstones were found in the third, there was nothing to suggest recent acute inflammation.

Histopathology of the 17 inflamed gallbladders confirmed acute inflammation with areas of total mural necrosis in some instances. Moreover, the intramural mass demonstrated on one tomogram was found at laparotomy to be a carcinoma in an inflamed gallbladder. This patient died 2 days later from a massive pulmonary embolus and autopsy confirmed the operative and radiological findings.

Discussion

The diagnosis of acute cholecystitis is often difficult to make and substantiate. Whereas acute appendicitis often poses similar problems of diagnosis, operation is usually simple and most surgeons would err on the side of caution and accept removal of some normal appendices rather than overlook acute inflammation. However, cholecystectomy is a major operation and patients with acute cholecystitis are usually middle aged or elderly; therefore , misdiagnosis at operation is seldom an acceptable risk. The incidence of faulty diagnosis varies from 6·0 per cent, reported by McCubbrey and Thieme (1959), who defend a conservative management policy, to as much as 33 per cent, reported by Holden et al. (1952). Halasz (1975) analysed 238 patients with a clinical diagnosis of acute cholecystitis and noted that in 47 patients (20 per cent) conditions other than cholecystitis were ultimately found. These included: renal problems 38 per cent (18 of 47), liver pathology 25 per cent, acute pancreatitis 21 per cent, appendicitis 11 per cent and pulmonary inflammatory disease 4 per cent. Fifty-seven of 191 patients underwent early operation and 5 (9 per cent) were found to have other pathology masquerading as acute cholecystitis. The remaining 134 had gallbladder disease confirmed radiologically at a later date. Furthermore, only two-thirds of patients with acute cholecystitis present with the typical clinical symptoms and signs (Staniland et al., 1972). With regard to management, the few controlled investigations that have been reported indicate that conservative and planned early surgical management of acute cholecystitis both carry much the same mortality and morbidity (van der Linden and Sunzel, 1970; Raine and Gunn, 1975; McArthur et al., 1975). With the likelihood of increasing recourse to early surgical management of the disease the need for a reliable objective investigation becomes paramount.

In a canine model, Moncanda et al. (1977) demonstrated by autoradiography that ^{125}I-labelled contrast material was taken up by inflammatory cells, both intravascularly and in the oedematous tissues of an inflamed gallbladder wall, while it remained confined to the vessel in a normal gallbladder. It was thought that the hyperaemia with tissue fluid equilibration of contrast material together with contrast-laden inflammatory cells was responsible for the curvilinear opacity noted when infusion tomography is performed in the presence of an inflamed gallbladder as described by Love (1976). However, Morin et al. (1977) pointed out that in 63 of 2867 patients (2·2 per cent) undergoing intravenous urography, incidental visualization of an opacity in the right hypochondrium was noted. This was thought to represent the gallbladder wall although none of these patients had symptoms of gallbladder dyspepsia or evidence of inflammation.

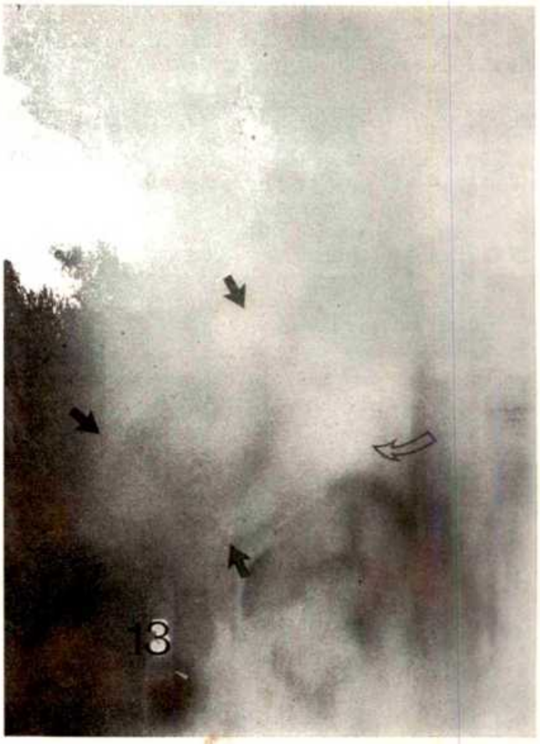

Fig. 2. Closed arrows demonstrate the curvilinear opacity and the open arrows show the intramural thickening mainly in the fundus. This was diagnosed radiologically as carcinoma in an inflamed gallbladder.

In this series of 21 patients positive infusion cholecystograms were obtained in 18 patients, the remaining 3 being negative. Of these patients one was shown to have an active peptic ulcer, one remains undiagnosed and one was shown to have gallstones at the elective operation. It may be that this patient had a mild attack of cholecystitis which rapidly subsided, but it may equally be that the symptoms were caused by some other condition as yet undiagnosed and the presence of gallstones was fortuitous.

Seventeen of the 18 patients who underwent operation after a positive infusion cholecystogram had acute inflammation of the gallbladder at laparotomy which was confirmed by histology. Review of the tomogram of the eighteenth patient showed that, although opacification was present in the region of the gallbladder, it was a diffuse opacification and not a curvilinear rim opacification as seen in acute inflammation. This was an error in interpretation rather than a false positive. Greater experience with the technique should improve interpretation and minimize the number of false positives. A clinical misdiagnosis was therefore made in 4 of the 21 patients (19 per cent). Acute renal problems masquerading as acute cholecystitis are often misdiagnosed according to Halasz (1975). The technique of infusion tomography lends itself well to the ruling out of this particular error of diagnosis as the kidney and pelvicaliceal systems are also demonstrated if a plain radiograph of the abdomen is taken after the infusion.

References

ECKELBERG M. E., CARLSON H. C. and MCILRATH D. C. (1970) Intravenous cholangiography with intact gall bladder. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **110**, 235–239.

EDITORIAL (1976) Treatment of acute cholecystitis. *Lancet* **1**, 182–183.

HALASZ N. A. (1975) Counterfeit cholecystitis. A common diagnostic dilemma. *Am. J. Surg.* **130**, 189–193.

HOLDEN W. D., CEBUL F. A. and LONGHRY C. W. (1952) Management of acute disorders of the biliary tree. *JAMA* **148**, 879–884.

LOVE L. (1976) Infusion tomography of the gallbladder. *Semin. Roentgenol.* **11**, 181–184.

MCARTHUR P., CUSCHIERI A., SELLS R. A. et al. (1975) Controlled clinical trial comparing early with interval cholecystectomy for acute cholecystitis. Initial study of 32 patients. *Br. J. Surg.* **62**, 850–852.

MCCUBBREY D. and THIEME T. (1959) In defence of the conservative treatment of acute cholecystitis with an evaluation of the risk. *Surgery* **45**, 930–936.

MEIRE H. (1978) Personal communication.

MORIN M. E., BAKER D. A. and MARSAN R. E. (1977) Visualization of the gall bladder wall at excretory urography. Implication for infusion tomography of the gallbladder. *Diagn. Radiol.* **125**, 35–38.

MUJAHED Z., EVANS J. A. and WHALEN J. P. (1974) The nonopacified gallbladder or oral cholecystography. *Radiology* **112**, 1–3.

RAINE P. A. M. and GUNN A. A. (1975) Acute cholecystitis. *Br. J. Surg.* **62**, 697–700.

STANILAND J. R., DITCHBURN J. and DEDOMBAL F. T. (1972) Clinical presentation of acute abdomen. Study of 600 patients. *Br. Med. J.* **3**, 393–398.

THORPE C. D., OLSEN W. R., FISCHER H. et al. (1973) Emergency intravenous cholangiography in patients with acute abdominal pain. *Am. J. Surg.* **125**, 46–50.

VAN DER LINDEN W. and SUNZEL H. (1970) Early versus delayed operation for acute cholecystitis, a controlled clinical trial. *Am. J. Surg.* **120**, 7–13.

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Operative choledochoscopy

A. KAPPAS, J. ALEXANDER-WILLIAMS, M. R. B. KEIGHLEY AND G. T. WATTS*

SUMMARY

We have reported the results of 121 examinations with the rigid choledochoscope performed by 13 different surgeons between 1969 and 1977. Pre-exploratory choledochoscopy was performed in 48 patients with a diagnostic accuracy of 94 per cent.

Post-exploratory choledochoscopy was used in 73 patients to define whether the common bile duct had been adequately cleared of stones. Fifty-one patients were correctly assessed as having a clear duct and unsuspected residual calculi were demonstrated by choledochoscopy in 13 patients. However, choledochoscopy failed to identify 9 patients with retained stones. The accuracy of post-exploratory choledochoscopy alone was 87 per cent and the accuracy of post-exploratory cholangiography was 82 per cent, but when choledochoscopy was combined with post-exploratory cholangiography there were no errors. We conclude that the addition of choledochoscopy to conventional radiological techniques is likely to reduce the incidence of residual calculi after choledochotomy.

RETAINED stones in the biliary tree after bile duct operations continue to embarrass and concern surgeons. In the literature, the reported incidence of retained stones ranges from 1·9 per cent (Nora et al., 1977) to 14 per cent (Hall et al., 1973). Although non-invasive techniques can be used for the postoperative removal of overlooked stones through the T tube track (Burhenne et al., 1974) or by endoscopic papillotomy (Classen and Demling, 1974), the aim should be to prevent stones being left behind at the time of operation.

On-table cholangiography before duct exploration and via a T tube after exploration has been shown to reduce the incidence of retained stones after biliary operations (Havard, 1970). However, both radiological techniques are subject to errors of interpretation and technical failures (Hall et al., 1973). Choledochoscopy is an alternative diagnostic technique applicable before and after duct exploration (Longland, 1973). Schein and colleagues (1963) proposed that on-table cholangiography should always be combined with choledochoscopy, but this practice has not gained widespread acceptance. Most reports of good results with choledochoscopy have been from individual surgeons with particular interest and expertise (Finnis and Rowntree, 1977). This experience does not necessarily reflect what should be the expectation of any general surgeon having to deal with biliary disease. We feel that it is important to document the results of choledochoscopy in the hands of all surgeons who perform cholecystectomy, whether they are experienced consultants or trainee registrars.

The development of fibreoptic instruments has renewed an interest in choledochoscopy, but the flexible fibreoptic choledochoscope has presented difficulties in manipulation (Shore et al., 1971), sterilization and image reproduction (Nora et al., 1977). Despite a recent report of excellent results with the flexible choledochoscope (Finnis and Rowntree, 1977), we and others have found the rigid choledochoscope to be more acceptable and easier to handle (Griffin, 1976). The rigid choledochoscope is a right-angled instrument with a lens system allowing visualization of objects from infinity to within almost direct contact with the lens. The instrument has a light-gathering element, an infusion channel and biopsy attachment. To view the duct system it is necessary to distend the bile duct with a continuous flow of saline.

Patients and methods

We have assessed the effectiveness of choledochoscopy from a study of 110 patients having 121 duct explorations during the years 1969–77. Choledochoscopy was used by a total of thirteen surgeons in all six surgical firms in our hospital. Choledochoscopy was performed before and/or after duct exploration using a rigid right-angled instrument (Storz 280 22A [Rimmer]).

The choledochoscope was inserted into the supraduodenal common bile duct through a 0·5-cm choledochotomy incision between stay sutures after mobilization of the peritoneum lateral to the second part of the duodenum. The stay sutures were crossed over one another to secure a reasonably watertight closure over the choledochoscope whilst the irrigation fluid was infused into the duct. The proximal common hepatic ducts were visualized first and the choledochoscope was reinserted for examination of the distal bile duct and ampulla, which was normally recognized by frond-like projections from the mucosa. The choledochoscope was sterilized in Cidex for 10 min between examinations and then rinsed in warm water. The eyepiece was cleaned with povidone-iodine.

Pre-exploratory choledochoscopy was used in 48 cases either instead of or as well as on-table cholangiography. Post-exploratory choledochoscopy was used in 73 cases to check that all stones had been removed or to confirm a negative conventional duct exploration. A final diagnosis of bile duct stones was based upon the following criteria: (*a*) positive findings during duct exploration; (*b*) filling defect seen on postoperative T tube cholangiography; or (*c*) demonstration of retained stones during annual clinical and biochemical follow-up.

Results

Accuracy of pre-exploratory choledochoscopy

Forty-eight choledochoscopies were performed before exploration of the duct and the procedure was used as the predominant method for diagnosing choledocholithiasis. On-table cholangiography was used in only 15 of these patients. Choledochoscopy indicated that the duct was clear in 36 cases (12 with negative on-table cholangiography) but in 3 of them stones were later demonstrated in the distal common bile duct by T tube cholangiography or repeat operation (2 of these 3 patients had negative on-table cholangiography). The presence of stones was demonstrated by choledochoscopy in 12 cases (3 with positive on-table cholangiography) and in all of them calculi were subsequently extracted from the duct. Furthermore, choledochoscopy correctly identified

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Table I: PRE-EXPLORATORY CHOLEDOCHOSCOPY

Endoscopic findings		Final diagnosis		Comment	
Clear ducts	36	Clear ducts	33	Correct	33
Choledocholithiasis	12	Choledocholithiasis	12	Correct	
Total	48	Total correct	45	Accuracy	

Table II: POST-EXPLORATORY CHOLEDOCHOSCOPY

Endoscopy findings		Final diagnosis		Comment	
Clear ducts	60	Clear ducts	51	Correct	51
		Retained stones	9	False negative	9
Unsuspected retained stones	13	Retained stones	13	Correct	13
Total	73	Total correct	64	Accuracy	87%

the number of stones present in 10 of the 12 patients. The overall accuracy for pre-exploratory choledochoscopy was 94 per cent and there were no false positive findings (*Table I*).

Accuracy of post-exploratory choledochoscopy
Seventy-three choledochoscopies were performed after exploration of the common bile duct and in these cases post-exploratory T tube cholangiography was used in 29 patients. The endoscope findings indicated that the duct had been adequately cleared of stones in 60 cases (21 with negative post-exploratory T tube cholangiography but 3 with positive findings). In 9 of these cases, however, post-exploratory cholangiography (3 cases) or subsequent T tube cholangiography (6 cases) demonstrated residual common bile duct calculi. Of the 9 patients with false negative choledochoscopy findings, 6 had retained stones in the distal common bile duct whilst in 3 the stones were located in the intrahepatic branches. The presence of retained stones was demonstrated by choledochoscopy in 13 patients in whom the surgeon had considered the ducts to have been satisfactorily cleared after conventional duct exploration (5 of whom had had negative post-exploratory T tube cholangiography). The overall accuracy of post-exploratory choledochoscopy was 87 per cent (*Table II*). The accuracy of post-exploratory cholangiography was 83 per cent, but when choledochoscopy was combined with cholangiography there were no errors.

Complications of choledochoscopy
There was one patient with infected bile (10^5 counts/ml of *Escherichia coli*) who became hypotensive and oliguric within 24 h of operation due to septicaemia from *E. coli*. In this patient high infusion pressures were necessary in order to clear the duct of debris before choledochoscopy. There were 13 cases of wound infection (11 per cent), and one case each of mild postoperative pancreatitis, clinical cholangitis and postoperative jaundice. All were treated successfully by conservative management.

Two patients, both over the age of 80, died in hospital following operation, one from pulmonary embolism and the other from renal failure. At postmortem there was no detectable trauma to the bile ducts caused by the choledochoscope and no residual calculi were found.

es there remains a small incines following choledocholithos in common duct instrumentaholangiography (Hall et al., e probably reflects individual tensive experience. It is imestrict the performance of to very experienced surgeons, and st be placed on adjunctive procedures (Sh and Shore, 1970).

In some centres the routine use of the rigid choledochoscope has reduced the incidence of retained stones to below 2 per cent (Nora et al., 1977). In our series 13 general surgeons, including registrars under training, have performed 121 choledochoscopies; the incidence of retained stones in this series was 6·6 per cent. We noticed, however, that most of the cases with retained stones occurred in the early period of the study when the participants first started to use choledochoscopy.

The majority of patients having pre-exploratory choledochoscopy did not have a conventional ontable cholangiogram and a small supraduodenal choledochotomy was performed for choledochoscopy. If the results of endoscopy were normal, primary duct suture was performed. The experience of choledochoscopy in these patients has provided us with the opportunity to examine the accuracy of this procedure. However, the results of careful on-table cholangiography (Schulenburg, 1969), particularly when combined with contact cholangiography (Hugh and Campbell, 1976), are so good that choledochotomy should not now be necessary for diagnosing or excluding choledocholithiasis. In view of the known hazards from sepsis of opening the common bile duct, even when the duct does not contain calculi (Keighley and Graham, 1971), we do feel that pre-exploratory choledochoscopy is necessary in the presence of normal on-table cholangiography findings.

The use of choledochoscopy after choledochotomy has been shown to be effective in avoiding residual stones in 11 of our patients (19 per cent). However, in our hands there were 9 other patients in whom residual calculi were missed by post-exploratory choledochoscopy, usually when the surgeon had only little choledochoscopic experience. Fortunately, in 5 of these cases stones were demonstrated by the post-exploratory T tube cholangiogram. Because of these results most of our surgeons now adopt the policy of performing both cholangiography and choledochoscopy after duct exploration. It is disappointing but not surprising to find that our results using the rigid choledochoscope are inferior to those reported by one enthusiast using the flexible instrument (Finnis and Rowntree, 1977). The disadvantages of flexible choledochoscopy are that the instrument requires considerable endoscopic expertise, it is difficult to sterilize, easy to damage and very costly to repair. It is thus an unsatisfactory instrument for most surgical units and unlike the rigid choledochoscope cannot be recommended as standard equipment for every district general hospital.

Choledochoscopy does not appear to increase the morbidity of biliary surgery provided that the irrigation fluid is not introduced under high pressure. In this study saline was usually delivered at a pressure of between 70 and 80 mmHg. Higher pressures have [illegible] sepsis in [illegible] series — [illegible] less than the normal rate of seps[illegible] [illegible]gst patients having a choledochotomy [illegible]hout antibiotic cover (Keighley, 1977). Nevertheless, most surgeons using the choledochoscope considered that patients were at risk from endogenous wound sepsis, and prophylactic antibiotics were recorded as being given to 84 (76 per cent) of the patients either before or during the operation.

Choledochoscopy in our series has proved to be safe for the patient and easy for the theatre staff. Progressive experience in the use of the procedure should reduce the incidence of retained common bile duct stones, particularly if it is combined with post-exploratory cholangiography.

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References

BURHENNE J. H., RICHARDS V., MATHEWSON C. et al. (1974) Non-operative extraction of retained biliary tract stones requiring multiple sessions. *Am. J. Surg.* **128**, 288–292.

CLASSEN M. and DEMLING L. (1974) Endoskopische Sphinkterotomie der Papilla Vateri und Steinextraktion aus dem Ductus Choledochus. *Deutsch. Med. Wochenschr.* **99**, 496–502.

[illegible]INNIS D. and ROWNTREE T. (1977) Choledochoscopy in exploration of the common bile duct. *Br. J. Surg.* **64**, 661–664.

[illegible]N T. W. (1976) Choledochoscopy. *Am. J. Surg.* **132**, 697–698.

[illegible]L R. C., SAKIYALAK P., KIM S. K. et al. (1973) Failure of operative cholangiography to prevent retained common duct stones. *Am. J. Surg.* **125**, 51–63.

[illegible]ON J. C. (1956) An electron microscope study of the [illegible]tic uptake and excretion of submicroscopic particles [illegible]jected into the blood stream and into the bile duct. *Acta Anat.* **32**, 262–291.

HAVARD C. (1970) Operative cholangiography. *Br. J. Surg.* **57**, 797–807.

HUANG T., BASS J. A. and WILLIAMS R. D. (1969) The significance of biliary pressure in cholangitis. *Arch. Surg.* **98**, 629–632.

HUGH T. B. and CAMPBELL T. J. (1976) Contact cholangiography. *Am. J. Surg.* **132**, 562–564.

KEIGHLEY M. R. B. (1977) Micro-organisms in the bile: a preventable cause of sepsis after biliary surgery. *Ann. R. Coll. Surg.* **59**, 329–334.

KEIGHLEY M. R. B. and GRAHAM N. G. (1971) Infective complication of choledochotomy with T tube drainage. *Br. J. Surg.* **58**, 764–769.

LONGLAND C. J. (1973) Choledochoscopy in choledocholithiasis. *Br. J. Surg.* **60**, 626–628.

NORA P. F., BERCI G., DORAZIO R. A. et al. (1977) Operative choledochoscopy: results of a prospective study in several institutions. *Am. J. Surg.* **133**, 105–110.

SCHEIN C. J., STERN W. Z., HURWITT E. S. et al. (1963) Cholangiography and biliary endoscopy as complementary methods of evaluating the bile ducts. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **89**, 864–875.

SCHULENBURG C. A. R. (1969) Operative cholangiography: 1000 cases. *Surgery* **65**, 723–739.

SHORE J. M., MORGENSTERN L. and BERCI G. (1971) An improved rigid choledochoscope. *Am. J. Surg.* **122**, 567–578.

SHORE J. M. and SHORE E. (1970) Operative biliary endoscopy: experience with the flexible choledochoscope in 100 consecutive choledocholithotomies. *Ann. Surg.* **171**, 269–278.

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Modified surgical procedures in intestinal tu

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SUMMARY

The results of modified surgical procedures in intestinal tuberculosis in 79 patients are presented. Special emphasis is laid on the role of limited ileocaecal resection and ileoplasty. These procedures are safe, quick and easy with preservation of functional portions of the bowel. They are of immense value in emergencies in chronically ill and emaciated patients.

INTESTINAL tubercular lesions are often multiple and may present either with chronic insidious onset, subacute or acute intestinal obstruction or with perforation. The treatment is complicated because of the associated widespread peritoneal involvement, massive and often caseous mesenteric lymphadenitis, multiplicity of lesions and extra-abdominal disease with its systemic effects.

Before the invention of anti-tubercular drugs these lesions were treated by short-circuiting procedures such as ileoileostomy and ileotransverse colostomy (Aird, 1957). With the availability of specific drugs, the aim of the surgical approach shifted towards local extirpation of the disease with wide ileal resections, right radical hemicolectomies and combinations of these procedures (Anand and Phatak, 1961; Abrams and Holden, 1964; Bhansali and Desai, 1968; Byrons and Mann, 1969). Recognizing the complications, side effects, limited applicability and the risks involved, simple procedures such as limited ileocaecal resections and 'strictureplasties' have evolved. Here the aim is to overcome the complications with preservation of as large a portion of functional bowel as possible. Short-circuiting procedures are used only in duodenal tuberculosis. Segmental resection of the small bowel is adopted only when multiple strictures are close together.

Patients and methods

This report consists of our experience with various surgical procedures in 79 cases of intestinal tuberculosis. This study does not include cases of gastric tuberculosis, isolated appendicular tuberculosis, colonic tubercular lesions distal to the ileocaecal region and those cases in which only biopsy was done because of miliary lesions, extensive adhesions and matting.

Ileocaecal lesions

Ileocaecal resections: Ileocaecal tubercular lesions are usually hypertrophic and involve variable portions of terminal ileum, caecum and ascending colon. Usually these lesions are associated with a group of enlarged and sometimes caseous lymph nodes in the ileocaecal angle. Occasionally the chain of lymph nodes extends to the origin of the superior mesenteric vessels, in which case there are usually multiple lymph nodes in the ileal mesentery. This was the sole lesion in 26 patients. In these patients treatment consisted of mobilization of the ileocaecal region and limited resection extending for 5 cm on either side of the lesion with end-to-end ileocolic anastomosis. The abdomen was closed after reperitonealization.

Ileal lesions

Early lesions: Very early lesions were better left alone. Only biopsy of the regional mesenteric lymph node was done to confirm the diagnosis and no complications were seen following biopsy in 6 cases.

Ileal resections: Multiple ileal short segment of bowel were treated by ex of the bowel bearing the lesions. In the early one or two isolated lesions were also treated by e end-to-end anastomosis. With increa experience plasty, however, this procedure wa only for multip lesions in a short segment of bowe

Bypass procedures: Th was used in 3 cases of duodenal tuberculosis. Gastrojejunostomy was the procedure used.

Ileoplasty: The tubercular lesions of small bowel, which were often multiple (from 2 to 19 lesions in an individual), were treated by ileoplasty. The bowel was opened longitudinally on the antimesenteric side across the lesion extending the incision on either side of the lesion. A portion was trimmed from the edge of the lesion for biopsy and the bowel was closed transversely in two layers. Even in tubular lesions, long loop ileoplasties were done. In granulomatous conditions, an oval or rhomboid portion of the lesion was excised on the antimesenteric side with its long axis in the line of the bowel and the defect was closed transversely. Even when perforation had occurred, an ileoplasty was performed, the perforation being included in the rhomboid or oval portion. In some cases this suture line was reinforced with a patch of omentum. In 32 patients, 59 ileoplasties were done, the maximum being eight ileoplasties in one individual. In every case a regional mesenteric lymph node was removed for biopsy.

Nineteen patients underwent a combination of these procedures. Six had ileocaecal resection and ileal resection, 8 had ileocaecal resection and one or more ileoplasties and 5 had ileal resection and ileoplasties.

Results

All the patients received antitubercular drugs for 6–18 months postoperatively. All patients were followed up for 6 months to 7 years. There were 2 deaths in the series. Two patients who had undergone resection developed faecal fistulas. Both patients recovered well on a conservative regimen under cover of antitubercular drugs. One patient who had undergone ileoplasty was re-explored after 6 months for obstruction due to an omental band. At that time the ileoplasties had healed.

Only a few glands in the mesentery were involved by tuberculosis. One female patient reported after 2 years for uterine leiomyoma. She had undergone resection for ileal strictures. Both the anastomotic sites had healed well and there was no trace of tuberculosis in the abdomen or pelvis (*Table 1*).

Discussion

The surgical treatment of intestinal tuberculosis has gone through many phases. Bypassing the stenosed segment either by enteroenterostomy or by ileotransverse colostomy was practised in the pre-antibiotic era (Aird, 1957). This practice has two main disadvantages; it is likely to produce a blind loop syndrome and the strictures in the remaining segments may produce fistulas or recurrent obstructions (Faulkner, 1964).

With the advent of specific antituberculous drugs, tuberculosis of the intestine was treated in a more radical fashion either by right hemicolectomy with or

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Table I: SURGICAL PROCEDURES AND COMPLICATIONS

Procedure	No. of cases	Complications Death	D.W.H.	F.F.	I.H.	R.O.
Biopsy	6			—	—	—
Ileocaecal resection	26		–	—	—	—
Bypass	3	—	—	—	—	—
Ileal resection	6	—	1	2	—	—
Ileoplasty	1[illegible]	—	2	—	1	1
Ileocaecal resection + ileal resection		[illegible]	2	—	—	—
Ileal resection + ileoplasty	5	—		—	1	—
Ileocaecal resection + ileoplasty	8	1	1	—	—	—
Total	79	2	7	2	2	1

D.W.H., delayed wound healing; F.F., faecal fistula; I.H., incisional hernia; R.O., recurrent obstruction.

without extensive removal of the lymph nodes for ileocaecal tuberculosis, or by wide resection for intestinal tuberculosis (Anand and Phatak, 1961; Abrams and Holden, 1964; Bhansali and Desai, 1968; Byrons and Mann, 1969). These procedures had the advantages of eradicating the disease locally.

These extensive and often multiple procedures may not be tolerated by a patient who is hypoprotinaemic, anaemic and toxaemic, or by a patient presenting with a perforation. Moreover, the lesions are often widely spaced and not suitable for resection without causing loss of normal bowel. Tuberculous perforations are usually associated with strictures (Bhansali and Desai, 1968). These patients may not tolerate a single resection. Simple suture of the perforation with drainage of the peritoneal cavity as advocated by Prakash (1975) has limited application.

Limited resection of the ileocaecal region for tuberculosis was advocated by Dutta Gupta in 1958 and Sharma and Mehta in 1964. It can be done through a relatively small incision and requires less mobilization of the colon, thus avoiding injuries to the ureter, kidney and duodenum. It is safe, quick and a comparatively easy procedure, suitable for use in an emergency. These merits have been specifically emphasized by Singh et al. (1973) and Joshi (1976). This limited resection can be used in all cases of ileocaecal tuberculosis irrespective of the degree of obstruction and stage of the disease. Tuberculous lesions of the small intestine with minimal obstruction should be left alone. They are unlikely to cause trouble. A segment of the intestine bearing multiple lesions is best treated by resection with end-to-end anastomosis provided the patient's condition permits.

In multiple lesions two criteria are used for selection of lesions for enteroplasty, the more important being the degree of reduction of the lumen. If the lumen is reduced by half or more enteroplasty is always selected. If the reduction of the lumen is not so great, the decision is based on the number of lesions that need enteroplasty and also the fitness of the patient. We have done eight enteroplasties in an individual. The second criterion is the degree of proximal hypertrophy of the bowel. In tubular lesions causing obstruction a long loop ileoplasty gives excellent results.

In hypertrophic granulomatous lesions the disease is more on the antimesenteric side of the bowel, with a pad of fat on the mesenteric side. In these patients an oval or rhomboid excision of the lesion on the antimesenteric side of the bowel with transverse anastomosis gives excellent results. This excision can also encircle the associated perforation.

References

ABRAMS J. S. and HOLDEN W. D. (1964) Tuberculosis of the gastrointestinal tract. *Arch. Surg.* **89**, 282–293.

AIRD I. (1957) *Companion in Surgical Studies*, 2nd ed. Edinburgh, Livingstone, p. 577.

ANAND S. S. and PHATAK I. C. (1961) Surgical treatment of abdominal tuberculosis with special reference to ileocaecal tuberculosis. Report of 100 cases treated surgically. *J. Ind. Med. Assoc.* **37**, 423–429.

BHANSALI S. K. and DESAI A. N. (1968) Abdominal tuberculosis. Review of 135 cases. *Ind. J. Surg.* **30**, 218–232.

BYRONS H. B. and MANN C. V. (1969) Clinical features and surgical management of ileo-caecal tuberculosis. *Proc. R. Soc. Med.* **62**, 1230–1233.

DUTTA GUPTA A. K. (1958) Intestinal tuberculosis. *Ind. J. Surg.* **20**, 396–400.

FAULKNER R. L. (1964) Tuberculosis as a surgical disease of the abdomen. *Ann. Surg.* **160**, 806–813.

JOSHI M. J. (1976) Conservative ileocaecal resection for diseases of the ileocaecal region. *Ind. J. Surg.* **38**, 255–260.

PRAKASH A. (1975) Acute tuberculous perforation of the small intestine. *Int. Surg.* **60**, 397–398.

SHARMA G. S. and MEHTA P. C. (1964) Ileo-caecal resections. *Ind. J. Surg.* **26**, 319–326.

SINGH H. N., ROY S. K. and VAIDYA M. P. (1973) Surgical treatment of ileocaecal tuberculosis—conservative versus radical resection. *Am. Surg.* **39**, 706–709.

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The value of different forms of treatment for varicose veins

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SUMMARY

In a controlled clinical investigation 516 patients with previously untreated saphenous varices were divided into three treatment groups according to a stratified group comparative design. The patients in treatment group 1 underwent a radical operation under full anaesthesia; the patients in group 2 were treated by means of minor operations followed by injection/compression therapy; the patients in group 3 were treated by means of injection/compression therapy alone. The results were evaluated both objectively and subjectively 3 months and 3 years after treatment, the follow-up being 100 per cent and 98·1 per cent complete at those times. With regard to the period of disability among those patients with jobs outside the home (63·8 per cent), there was a statistically significant difference between the three groups, the median period of disability being 14·2, 7·6 and 0 days respectively. In all three treatment groups the results were worse after 3 years than after 3 months, but the difference was significantly less following radical operation than after combined treatment, and significantly less following combined treatment than after injection/compression therapy alone. The patients were randomized and treated by the author and the results of treatment were evaluated by the author and partly controlled by another investigator.

It is concluded that the primary treatment for incompetence of the saphenous veins should be a radical operation.

For more than a hundred years both operative treatment and sclerotherapy have been used for the treatment of varicose veins, and disagreement persists concerning the relative merit of and the indication for these two principal forms of treatment. Following a long period during which operative treatment clearly dominated, the international literature covering the past 15 years reveals an increasing enthusiasm for sclerotherapy as described by Fegan (1967) and Sigg (1976). In a number of publications, results apparently up to the standard of those following operative treatment have been reported (Reid and Rothnie, 1968; Chant et al., 1972; Stother et al., 1974; Doran and White, 1975), and it is maintained that outpatient sclerotherapy is not only more economical for the community but also more advantageous for the individual patient than operative treatment involving a period of stay in hospital (Piachaud and Weddell, 1972).

An attempt to evaluate and compare the different forms of treatment for varicose veins by use of the current literature is relatively fruitless. Despite many detailed classifications and definitions of varices (Borschberg, 1967), clinically the concept of varices covers a broad spectrum of venous complaints in the lower extremity, ranging from dilated venules, dilated superficial veins and varicose saphenous veins to severe post-thrombotic syndromes. It is obvious that different methods of selecting and composing the clinical material have a bearing on the results of treatment which can be obtained, and even a fair degree of certainty regarding the comparability of material is extremely rare.

The therapy employed is most frequently described in the literature as 'radical operation' or 'injection–compression therapy'. Not only do these descriptions cover individual conceptions of what the method involves, but sclerotherapy and operative treatment alike may be carried out with a greater or lesser degree of expertise, which changes the significance of the treatment.

In comparing results the period of observation after completion of treatment is important, because the number of unsatisfactory results following treatment is a function of the period of observation (van der Stricht, 1966).

In the current literature the results of treatment for varicose veins have been stated in countless ways. They may be based on an objective or subjective evaluation, each of which may be made according to numerous, differing criteria. Furthermore, despite well-defined criteria, two or more investigators may evaluate a given result differently (McAdam et al., 1976).

In an attempt to eliminate some of these difficulties, a controlled clinical investigation was started in Copenhagen in 1972 with the objective of comparing the results of three different forms of treatment for varicose veins. The treatment and the evaluation of the results have been carried out by the author according to well-defined principles and criteria.

Patients and methods

A series of 516 patients at the Copenhagen County Hospital in Glostrup who presented with saphenous varices, not previously treated, were registered with regard to sex, age, height and weight as well as the type and degree of varicosity. They were divided into three treatment groups according to a stratified group comparative design. Thirty-three patients left the study because they moved from the hospital area or because they sought treatment elsewhere during the period between the preliminary examination and the actual treatment in the hospital.

A subsequent analysis of the treatment groups showed that not only was there full comparability with regard to the chosen criteria, but also with regard to the duration of the illness, symptomatology and the other relations shown in *Tables I–V*.

Treatment

Group 1: The 161 patients in this group were admitted to hospital for about 30 h and underwent a radical operation under full anaesthesia. The operation consisted of flush ligation at the saphenofemoral and/or saphenopopliteal junction, extraction of the long and/or short saphenous vein, ligation of incompetent perforating veins located by clinical examination and avulsion of varicose tributaries by way of multiple small incisions. The mean number of incisions was 8·2 (range 2–17). The median duration of the operation was 34 min for unilateral varices and 68 min for bilateral varices.

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[illegible]	[illegible]	em	Male
[illegible]	[illegible]	133	28
[illegible]	[illegible]	133	32
3	157	124	33
Total	483 (100%)	390 (80·8%)	93 (19·2%)

No statistically significant difference.

Table II: DURATION OF ILLNESS*

Group	Duration (yr) 1–5	6–10	11–15	16–20	21–30	31–40	Median
1	41	50	22	29	15	4	9·5
2	50	51	31	12	15	6	8·7
3	32	54	36	21	7	7	9·8
Total	123	155	89	62	37	17	9·3

* Defined as from the time when the patient first became aware of varices.
No statistically significant difference.

Table III: SYMPTOMS AND SIGNS

	Group 1	2	3	Total
Restless legs	66·5	53·9	60·5	60·3
Fatigue	71·4	66·7	70·7	70·3
Oedema	47·8	37·6	40·8	42·0
Pain	50·3	47·9	52·9	50·3
Cramps	39·8	47·9	39·5	42·4
Cosmetic	80·1	78·8	79·6	79·5
Phlebitis	8·7	18·8	12·7	13·5
Thrombosis	7·5	4·2	3·2	5·0
Ulcer	5·0	1·2	1·3	2·5

The figures are percentages.
Information regarding phlebitis in the superficial veins was significantly rare in group 1 and significantly frequent in group 2. Previous occurrence of venous ulcer was significantly frequent in group 1. In no other respect was there any statistically significant difference between the three treatment groups.

Table IV: DISTRIBUTION OF PATIENTS WITH JOBS OUTSIDE THE HOME

Group	*n*	Jobs outside the home	%
1	161	105	65·2
2	165	110	66·7
3	157	93	59·2
Total	483	308	63·8

No statistically significant difference.

Table V: OBJECTIVE FINDINGS AT PRE-TREATMENT EXAMINATION OF INVOLVED EXTREMITIES

Group	Insufficiency of L.s.	L.s. +p.	L.s. & S.s.	L.s. & S.s. +p.	S.s.	S.s. +p.
1	52·8	36·0	4·4	3·1	2·5	1·2
2	61·2	22·4	8·5	2·4	3·6	1·8
3	62·4	22·3	6·4	4·5	4·5	0·0
Total	58·8	26·9	6·4	3·3	3·5	1·0

L.s., long saphenous vein; S.s., short saphenous vein; p., perforation.
All figures are percentages.
Clinical suspicion regarding incompetence of perforating veins was significantly more frequent in group 1 than in groups 2 and 3. In no other respect was there any statistically significant difference between the three groups.

Table VI: MEDIAN AND RANGE OBSERVATION PERIODS (mth) FOR THREE GROUPS

Group	1st review Median	Range	2nd review Median	Range
1	3·4	2–11	34·6	28–42
2	3·4	2–11	33·3	27–40
3	3·3	1–10	32·3	27–39

No statistically significant difference.

Table VII: RELATIONSHIP BETWEEN OBJECTIVE AND SUBJECTIVE EVALUATIONS OF TREATMENT

Group	Review	Evaluation	*P*
1	1st	Objective better than subjective	$0.05 > P > 0.01$
	2nd	Subjective better than objective	$P < 0.01$
2	1st	Objective better than subjective	$P > 0.05$
	2nd	Subjective better than objective	$P < 0.01$
3	1st	Subjective better than objective	$P < 0.01$
	2nd	Subjective better than objective	$P < 0.01$

Table VIII: DISTRIBUTION OF OBJECTIVE AND SUBJECTIVE EVALUATIONS OF TREATMENT AT 3-MONTH REVIEW

Evaluation	Group 1	2	3
Objective			
A+B	96·3	95·7	84·7
C+D	3·7	4·2	15·3
Subjective			
A+B	93·2	92·7	89·2
C+D	6·8	7·2	10·8

Classes A and B, satisfactory; classes C and D, unsatisfactory.
All figures are percentages.

Table IX: DISTRIBUTION OF OBJECTIVE AND SUBJECTIVE EVALUATIONS OF TREATMENT AT 3-YEAR REVIEW

Evaluation	Group 1	2	3
Objective			
A+B	89·8	65·2	36·6
C+D	10·2	34·8	63·4
Subjective			
A+B	93·0	84·8	70·5
C+D	7·0	15·2	29·5

Classes A and B, satisfactory; classes C and D, unsatisfactory.
All figures are percentages.

Group 2: 165 patients in group 2 were treated as outpatients by means of a combination of minor operations followed by postoperative transcutaneous injection/compression therapy. The operations were performed under local analgesia and consisted of flush ligation of the saphenofemoral and/or saphenopopliteal junction and ligation of incompetent perforating veins found by clinical examination.

Group 3: The 157 patients in this group were treated as outpatients by means of injection/compression therapy alone.

The technique used for sclerotherapy was that described in detail by Sigg (1976), and the sclerosant was Aethoxysklerol (hydroxypolyaethoxy-dodecan) in a 3 per cent solution.

Apart from a non-fatal pulmonary embolism occurring in a woman 14 days after bilateral radical operation, only minor complications were seen, and there was no statistically significant difference between the three groups as regards associated complications.

With regard to the period of disability experienced by those patients with jobs outside the home, there was a statistically significant difference between the three groups, the median period of disability being 14·2, 7·6 and 0 days respectively

Observation period and follow-up

The patients were examined and interviewed at th[illegible], at their work or in their home both 3 months and 3 [illegible]r completion of treatment (*Table VI*). At the secon[illegible] 5 patients had died from unrelated diseases and 3 patients were lost, the follow-up therefore being 100 per cent and 98·1 per cent complete at the respective times, without any statistically significant difference between the three groups.

Results of treatment

Treatment was evaluated both objectively and subjectively according to the following criteria:

Objective evaluation

Class A: No visible or palpable varices.

Class B: A few visible or palpable varices with diameter less than 5 mm.

Class C: Remaining or newly formed varices with diameter over 5 mm, main trunks and incompetent perforating veins eliminated.

Class D: Main trunks and/or incompetent perforating veins present.

Subjective evaluation

Class A: No inconvenience.

Class B: Slight functional or cosmetic imperfection, but satisfaction with the result.

Class C: Appreciable functional or cosmetic failure; an improvement compared with the condition before treatment, but dissatisfaction with the result.

Class D: Unaltered or greater inconvenience.

For statistical reasons the results of treatment were evaluated individually for each extremity and, in patients with bilateral varices, one extremity was eliminated by ballot. A Kruskal–Wallis test showed the results of radical operation at 3 years after treatment to be significantly better than those of combined treatment ($P < 0{\cdot}0005$) and combined treatment to be significantly better than sclerotherapy alone ($P < 0{\cdot}0005$).

Table VII shows the relationship between the objective and subjective evaluations, and *Tables VIII* and *IX* show the results of treatment at the first and second review in a simplified form.

Thirty-five patients were examined and interviewed independently by another investigator* whose evaluations were slightly more positive than the author's, but the relationship between [illegible] groups was exactly the same.

Discussion

The treatment has been carried out by a general surgeon with special interest in the treatment of venous disorders and experience in sclerotherapy, but it is not possible to define the degree of expertise with which the surgery and the sclerotherapy have been performed.

The period of observation is not significantly different with regard to the three groups. In all three groups the number of satisfying results of treatment declined between 3-month to 3-year follow-up, but the difference was significantly less for radical operation than combined treatment, and significantly less for combined treatment than sclerotherapy alone. There is no reason to assume that these relationships should change after a longer follow-up.

In a well-controlled trial Hobbs (1974) found similar results, and it can be concluded that saphenous varices are best treated by a radical operation, in spite of the fact that the period of disability following surgery is significantly longer than after sclerotherapy.

References

BORSCHBERG E. (1967) The prevalence of varicose veins. Basle Karger.

CHANT A. D. B., JONES H. O. and WEDDELL J. M. (1972) Varicose veins: a comparison of surgery and injection/compression sclerotherapy. *Lancet* **2**, 1188–1191.

DORAN F. S. A. and WHITE M. (1975) A clinical trial designed to discover if the primary treatment of varicose veins should be by Fegan's method or by an operation. *Br. J. Surg.* **62**, 72–76.

FEGAN G. (1967) *Varicose Veins: Compression Sclerotherapy.* London, Heinemann Medical.

HOBBS J. T. (1974) Surgery and sclerotherapy in the treatment of varicose veins. *Arch. Surg.* **109**, 793–796.

MCADAM W. A. F., HORROCKS J. C. and DE DOMBAL F. T. (1976) Assessment of the results of surgery for varicose veins. *Br. J. Surg.* **63**, 137–140.

PIACHAUD D. and WEDDELL J. M. (1972) Cost of treating varicose veins. *Lancet* **2**, 1191–1192.

REID R. G. and ROTHNIE N. G. (1968) Treatment of varicose veins by compression sclerotherapy. *Br. J. Surg.* **55**, 889–895.

SIGG K. (1976) *Varizen, Ulcus cruris und Thrombose*, 4th ed. Berlin, Springer-Verlag.

STOTHER I. G., BRYSON A. and ALEXANDER S. (1974) The treatment of varicose veins by compression sclerotherapy. *Br. J. Surg.* **61**, 387–390.

VAN DER STRICHT J. (1966) Technik und Indikationen der chirurgischen Behandlung von Varizen und ihrer Kombination mit Verödung. *Zentralbl. Phlebol.* **5**, 39–45.

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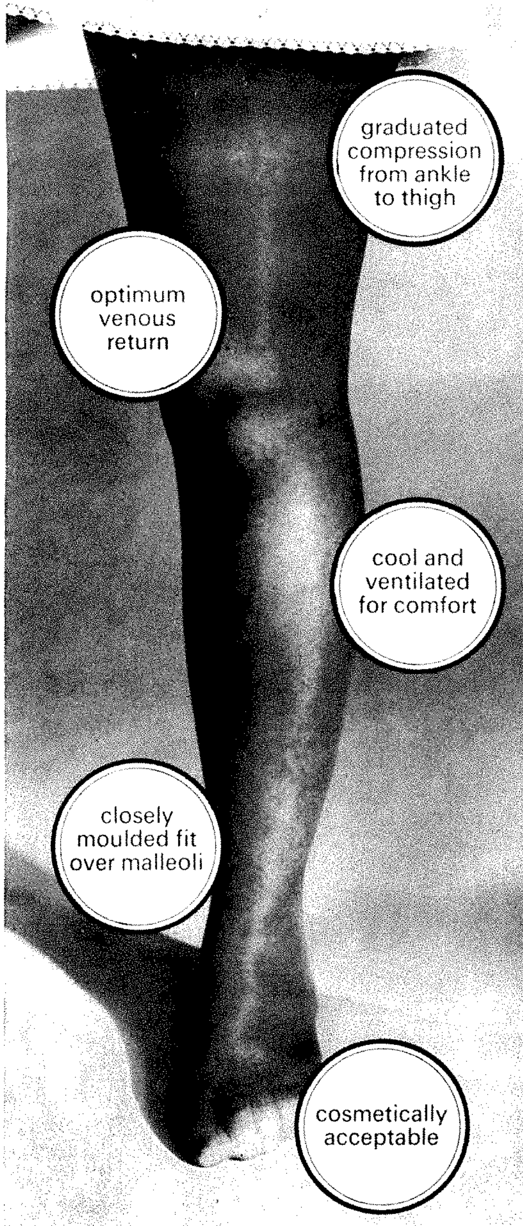
Varicose veins?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Br. J. Surg. Vol. 66 (1979) 185–187

[illegible] vity of varicose veins

[illegible] . BROWSE*

SUMMARY

The plasma fibrino[illegible] n, p[illegible] lytic ac[illegible] nolytic a[illegible] hand, g[illegible] forating veins ha[illegible] been stud[illegible] skin changes in the lower leg seco[illegible] sease (lipodermatosclerosis), [illegible] pa[illegible] with uncomplicated varicose veins and in [illegible] normal volunteers undergoing surgery. There was significantly more vein wall fibrinolytic activity in normal volunteers than in the patients with lipodermatosclerosis, not only in the ankle ($P < 0{\cdot}001$) but also in the hand ($P < 0{\cdot}05$).

It is suggested that the reduced tissue fibrinolytic activity is a causative factor in the skin changes and ulceration of the post-phlebitic leg, and that since the reduced activity is not confined to the leg, it may be a primary systemic defect rather than a state secondary to venous congestion.

IN 1959 Todd demonstrated that the vein wall is an important source of plasminogen activator, and modifications of his technique for measuring the vein wall fibrinolytic activity have been used in a number of subsequent studies of venous disease (Pandolfi et al., 1967).

It has been shown by Pandolfi et al. (1967) and by Browse, Gray et al. (1977) that the vein walls are deficient in fibrinolytic activity in patients with recurrent venous thrombosis, and Burnand et al. (1976) have shown that the prolonged venous hypertension in post-phlebitic lipodermatosclerosis causes leakage of fibrinogen through the capillaries and the development of an extravascular pericapillary fibrin 'cuff'.

The purpose of this study was to ascertain whether vein wall fibrinolytic activity in the peripheral veins of patients with venous incompetence is abnormal and whether it is related to the severity of the disease.

Patients and methods

Twenty patients with varicose veins have been investigated—10 with primary long saphenous incompetence and normal skin (mean age of 40 years) and 10 with severe lipodermatosclerosis (mean age of 55 years). Two patients from each group had previously suffered minor episodes of superficial thrombophlebitis in the legs. One patient with primary uncomplicated varicose veins gave a definite history of deep vein thrombosis. The patients with uncomplicated varicose veins had a shorter history of varicosities (mean 18·8 years) than the patients with skin changes (mean 29 years).

Normal veins were obtained from 17 patients (mean age 57) undergoing surgery for local diseases (e.g. gallstones, hernia, peptic ulcer) which, as far as we know, do not affect the vein wall fibrinolytic activity.

Patients with a history of arteriosclerosis of neoplastic disease and patients with a raised preoperative plasma triglyceride or cholesterol were excluded since these abnormalities are shown to be associated with abnormal fibrinolysis. The haemoglobin concentration, platelet count and erythrocyte sedimentation rate of all the patients studied were within the normal range.

A sample of venous blood was taken from the antecubital fossa to measure the plasma fibrinogen concentration and the dilute blood clot lysis time (DBCLT) on the morning following admission (between 9.30 and 10.0 a.m. with the patient fasting). Another sample of blood was taken after 10 min of venous [illegible]gestion using a pneumatic cuff inflated to a pressure of [illegible] Hg to measure 'fibrinolytic capacity' (Robertson et al., [illegible]

The plasma fibrinogen concentration was then estimated with the technique described by Ingram (1952) and DBCLT was measured by Fearnley's method (Fearnley et al., 1957).

Segments of vein 1 cm in length were removed with a minumum of trauma by one author (J. H. N. W.) after induction of general anaesthesia and before surgery. In this way any effects of anaesthesia were standardized. Specimens were taken from the hand, groin, knee and ankle veins of all 20 patients. In 15 patients segments were also removed from both competent and incompetent lower leg perforating veins, competence having been assessed by the Turner-Warwick or 'bleed back' test (Turner-Warwick, 1931). The other 5 patients did not have perforating vein exploration. In the control group the segments of vein were removed from the hand and foot and, at herniorrhaphy, from the groin.

The distal specimens were taken first to avoid distending the segment of vein to be biopsied before removal, since this is known to enhance fibrinolysis (Tighe and Swan, 1963). For the same reason hand vein biopsies were not taken from the arm used by the anaesthetist for recording blood pressure and administering drugs. Two specimens were taken from the groin of patients with varicose veins, one from the long saphenous vein and the second from an adjacent small tributary to see if the size of the vein affected the measurement of tissue fibrinolytic activity.

Vein wall fibrinolytic activity was scored by a modification of the Todd technique described by Browse, Gray et al. (1977). The maximum possible score was 54.

Since the variances differed the validity of using the Student's t test was checked using the variance ratio test. It was subsequently necessary to use the non-parametric Mann–Whitney U test when comparing vein wall activity in the foot (*see Fig.* 3) but in the other comparisons Student's t test was valid and used in preference. Differences between the results of the various groups were considered to be statistically significant if the P value was 0·05 or less.

The purpose of the experiment was explained to the patients and their written consent to venepuncture and vein biopsies obtained.

Results

Vein wall activity

The vein wall fibrinolytic activity in the biopsies taken from the 20 patients with varicose veins is shown in *Fig.* 1. There was a significant difference between the groin and ankle specimens ($P < 0{\cdot}01$). There was no significant difference between the activity of hand and groin specimens. The difference between the groin and knee specimens was significant ($P < 0{\cdot}01$).

Fig. 2 shows the vein wall fibrinolytic activity of these patients subdivided into those with lipodermatosclerosis and those with normal skin. It can be seen that the mean activity of the former was always lower than the mean activity of the latter. The difference at the ankle was significant ($P < 0{\cdot}01$). *Figs.* 1 and 2 also show that the fibrinolytic activity of the wall of the long saphenous vein gradually increases as it ascends to the groin.

Fig. 3 compares the foot vein fibrinolytic activity of those patients with varicose veins with that of the 17 normal subjects. There was a significant difference

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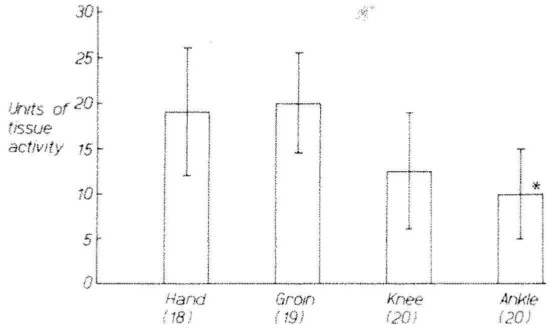

Fig. 1. Relationship between site and vein wall fibrinolytic activity in 20 patients with varicose veins (mean ± s.d.). * Significantly different from hand ($P < 0.01$) and groin ($P < 0.01$).

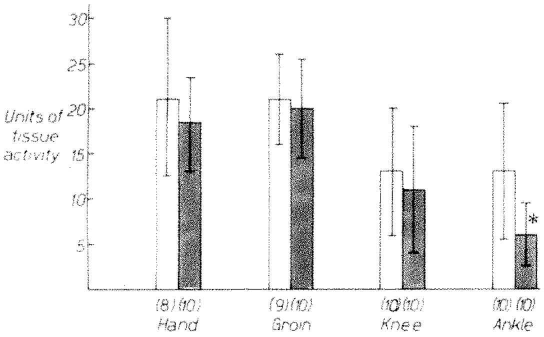

Fig. 2. Relationship between site and vein wall fibrinolytic activity in 20 patients with varicose veins, subdivided into those with (shaded) and those without (white) lipodermatosclerosis (mean ± s.d.). * Significantly different from ankle vein specimens in patients with uncomplicated varicose veins ($P < 0.01$).

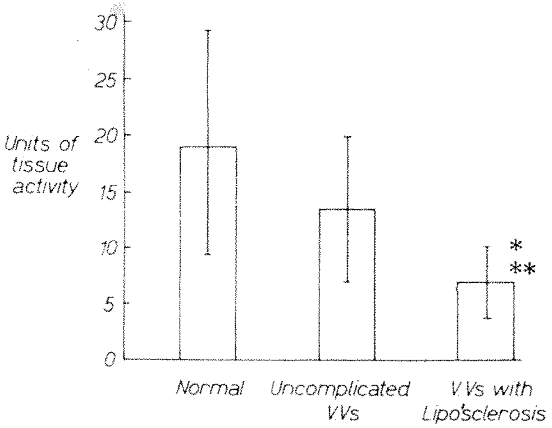

Fig. 3. Foot vein fibrinolytic activity in normal subjects and patients with complicated and uncomplicated varicose veins (mean ± s.d.). * Significantly different from normal ($P < 0.02$). ** Significantly different from uncomplicated varicose veins ($P < 0.05$).

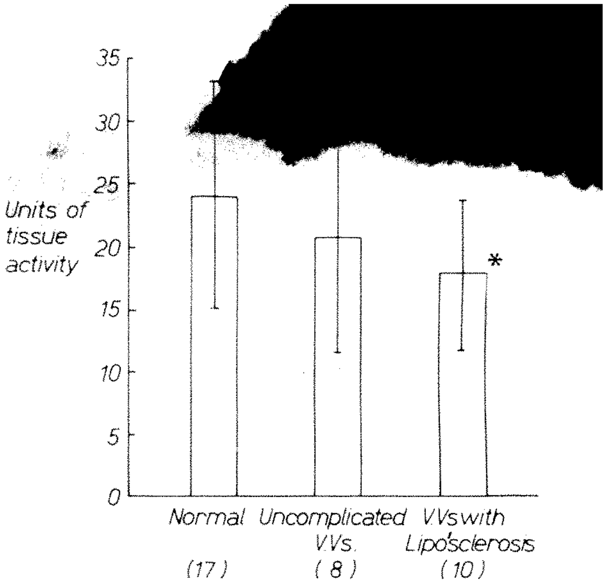

Fig. 4. Hand vein wall fibrinolytic activity in normal subjects and patients with complicated and uncomplicated varicose veins (mean ± s.d.). * Significantly different from normal ($P < 0.05$).

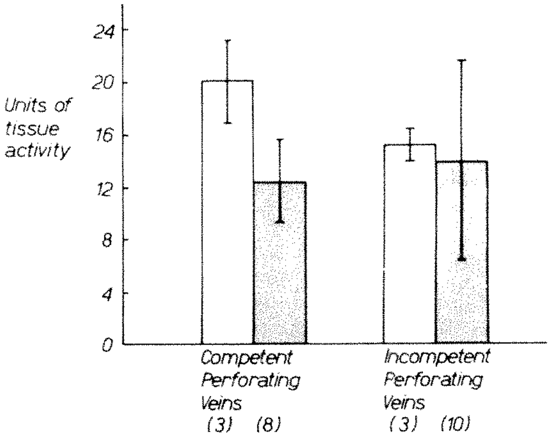

Fig. 5. Fibrinolytic activity of competent and incompetent perforating veins in 15 patients with complicated (shaded) and uncomplicated (white) varicose veins (mean ± s.d.).

between the patients with lipodermatosclerosis and the normal subjects ($P < 0.02$) and those with primary varicose veins ($P < 0.05$). It is of interest that a similar trend was seen in the hand (*Fig.* 4), although this only reached significance when comparing normal volunteers with patients with lipodermatosclerosis ($P < 0.05$).

Since the size of the veins being studied varied, we compared the activity of the main long saphenous vein in the groin (8 mm diameter) with the activity of a small tributary (2 mm diameter) at the same level (19 pairs). The mean activity of the tributaries was 23·4 units and of the long saphenous vein 20·3 units, a statistically insignificant difference. We therefore concluded that it was unnecessary to take into account the diameter of the vein when assessing the results.

Fig. 5 compares the fibrinolytic activity of competent and incompetent perforating veins obtained from patients undergoing a surgical exploration of these veins. There was no significant difference in activity between the two groups. The mean fibrinolytic activity of all incompetent perforating veins was 14·6 units, and of all competent perforating veins, 14·8 units. These values show that the perforating veins do not have any special degree of fibrinolytic activity and fit the general pattern of a graded reduction in activity towards the ankle, as shown in *Fig.* 1. We were unable to make a statistical comparison of the activity of the perforating veins in patients with uncomplicated varicose veins with that in patients with lipodermatosclerosis because of the small number of calf explorations carried out on the former group.

Blood fibrinolytic activity

There was no significant difference between the resting venous blood fibrinolytic activity in the arms of the patients with varicose veins and in the normal volunteers. The increase in arm blood fibrinolytic activity produced by venous congestion in the patients with lipodermatosclerosis and in those with uncomplicated varicose veins was the same. The mean fall in DBCLT in the former group was 54 per cent and in the latter group 52 per cent.

Discussion

These results show that patients with venous valvular incompetence have abnormal vein wall fibrinolytic activity and that this is related to the presence of the skin and subcutaneous tissue changes called lipodermatosclerosis. Burnand et al. (1976) have demonstrated a fibrin 'cuff' around the dermal capillaries in areas of lipodermatosclerosis and suggest that this layer of fibrin may be impervious and lead to tissue necrosis and ulceration. The development of the extravascular cuff of fibrin may be related to a primary pre-existing defect of tissue fibrinolysis, or to the depletion of a previously normal vein wall fibrinolytic activity following the prolonged leakage of fibrinogen from the capillaries and the body's attempt to clear it away.

The diminution of vein wall fibrinolytic activity is not localized to the involved leg. In patients with lipodermatosclerosis the vein wall activity in the hand is also reduced. This suggests that these patients have a primary generalized deficiency of vein wall fibrinolysis; or alternatively that the venous disease in one lower limb can deplete the plasminogen activator in the vein walls of the upper limb.

It is generally taught and believed that lipodermatosclerosis is a sequel to previous deep venous thrombosis. It may be that the deficiency in fibrinolysis plays a causative role in the original thrombosis.

Despite the reduced vein wall activity, the fibrinolytic response in the arm to venous occlusion was the same in the control and the test subjects. In previous studies of larger groups of patients, however, the arm venous blood fibrinolytic activity of patients with lipodermatosclerosis has been found to be below normal (Browse, Jarrett et al., 1977).

Prolonged venous hypertension secondary to valvular incompetence increases the tendency for fibrinogen to leak out of the capillaries and necessitates an increase in fibrinogen clearance from the interstitial spaces (Burnand et al., 1976). Since it is often impossible to cure the venous incompetence, treatment might be directed towards increasing the clearance of interstitial fibrin by stimulating the fibrinolytic system. It is well known that elevation of the limb accelerates the healing of venous ulceration, and Karaca and Nilsson (1971) have found that prolonged bed rest raises the level of leg vein wall fibrinolytic activity to a level similar to that of the arm. This might partially explain the beneficial effect of bed rest on venous ulceration. Stanozolol has been shown to enhance fibrinolysis and a preliminary report by Browse, Jarrett et al. (1977) suggests that this has therapeutic value in the treatment of post-phlebitic lipodermatosclerosis. Overall, there is increasing evidence that a deficiency of the fibrinolytic system plays a role in the aetiology of lipodermatosclerosis and it may be as important a causative factor as the abnormal venous hypertension.

References

BROWSE N. L., GRAY I., JARRETT P. E. M. et al. (1977) Blood and vein wall fibrinolytic activity in health and vascular disease. *Br. Med. J.* **1**, 478–481.

BROWSE N. L., JARRETT P. E. M., MORLAND M. et al. (1977) Treatment of liposclerosis of the lower leg by fibrinolytic enhancement: preliminary report. *Br. Med. J.* **2**, 434–435.

BURNAND K. G., CLEMENSON G., WHIMSTER I. M. et al. (1976) Extravascular fibrin deposition in response to venous hypertension—the cause of venous ulcers. *Br. J. Surg.* **63**, 660.

FEARNLEY G. R., BANFORT G. U. and FEARNLEY E. (1957) Evidence of diurnal fibrinolytic rhythm with a simple method of measuring natural fibrinolysis. *Clin. Sci.* **16**, 645–650.

INGRAM G. I. C. (1952) The determination of plasma fibrinogen by the clot weight method. *Biochem. J.* **51**, 583–585.

KARACA M. and NILSSON I. M. (1971) Fibrinolytic activity in hemiplegic patients. *Acta Med. Scand.* **189**, 325–329.

PANDOLFI M., ISACSON S. and NILSSON I. M. (1969) Low fibrinolytic activity in the walls of veins of patients with thrombosis. *Acta Med. Scand.* **186**, 1–5.

PANDOLFI M., ROBERTSON B., NILSSON I. M. et al. (1967) Fibrinolytic activity of human veins. *Lancet* **2**, 127.

ROBERTSON B. R., PANDOLFI H. and NILSSON I. M. (1972) Fibrinolytic capacity of healthy volunteers. *Acta Clin. Scand.* **138**, 429–432.

TIGHE J. R. and SWAN U. T. (1963) Fibrinolysis in venous obstruction. *Clin. Sci.* **25**, 219–222.

TODD A. S. (1959) The histochemical localization of fibrinolytic activation. *J. Pathol. Bacteriol.* **78**, 281–283.

TURNER-WARWICK W. (1931) *The Rational Treatment of Varicose Veins and Varicocoele.* London, Faber.

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Randomized controlled trial of cefuroxime for established postoperative respiratory infection

J. C. LITCHFIELD, M. R. B. KEIGHLEY, I. W. MYATT
AND M. C. EDWARDS*

SUMMARY

A randomized controlled trial has investigated the value of cefuroxime (a new antibiotic resistant to β-lactamase) in 80 patients with established postoperative respiratory infection. Although the majority of respiratory isolates were sensitive to cefuroxime, there was no significant advantage in the antibiotic group compared with the controls with respect to duration of fever, radiological abnormality or infected sputum. We conclude that antibiotics are rarely necessary for the majority of patients who develop postoperative respiratory infections.

POSTOPERATIVE respiratory sepsis and atelectasis are frequent complications of upper abdominal operations, particularly in the elderly, heavy smokers and patients with chronic bronchitis (Cahill, 1968; Weightman, 1968; Munro, 1970). It has been suggested that antibiotics might be useful in preventing these complications, but they only occur in a minority of patients. Little is known of the value of deferring antibiotic therapy until respiratory complications have become established (*British Medical Journal*, 1977). *Haemophilus influenza* and *Streptococcus pneumoniae* are the pathogens most frequently isolated from the respiratory tract after operation and they are usually sensitive to the broad spectrum penicillins and the cephalosporins (Cavanagh et al., 1976; O'Callaghan et al., 1976). The aim of this study has been to investigate whether antibiotics are of any value for the management of established postoperative respiratory infection. On account of the emergence of bacteria that destroy antibiotics by the production of β-lactamase (Howard et al., 1978), the antibiotic chosen for this trial was cefuroxime, which is resistant to destruction by β-lactamases (Gomme, 1977).

Patients and methods

Eighty consecutive patients who developed postoperative respiratory sepsis were studied. Two of the following three criteria were necessary for admission into the trial: fever greater than 38 °C, purulent sputum or evidence of a new radiographic abnormality compared with the preoperative chest radiograph. All patients received twice-daily chest physiotherapy (breathing exercises, frappage, postural drainage), but nebulizers, ventilators or oropharyngeal suction were not used. In addition to the physiotherapy regimen, 41 patients received cefuroxime while the remaining 39 were given no antibiotic (controls). The allocation of patients to cefuroxime or no antibiotic was based upon random numbers. Cefuroxime was given by intramuscular injection in a dose of 750 mg three times a day.

Response to therapy was evaluated by duration of fever, persistence of infected sputum and duration of radiographic abnormality. Sputum samples were cultured on the third and fifth day. Chest radiographs were repeated on the third and fifth day and were reported by a single radiologist who was unaware whether or not the patient was receiving cefuroxime. Assessment of respiratory function by vitalograph was abandoned because results were not reproducible after recent major surgery. A subjective assessment of response to therapy was also recorded by one of the physiotherapists who did not know into which group the patient had been allocated. Sputum was collected in sterile jars during physiotherapy. The mucus was digested by adding an equal volume of trypure-pancreatin mixture and cultured at 37 °C on blood agar. MacConkey's agar and chocolate agar under aerobic conditions only. Organisms were identified by Gram-stain, appearance of colonies and biochemical reactions. Samples of sputum were stored at 4 °C for batch antibiotic assay using the plate diffusion method.

Patients were excluded if any therapeutic antibiotic had been given before entry into the trial or if prophylactic antimicrobials had been used before or during operation.

Results

The treatment and control groups were similar with respect to criteria for entry into the trial—age, sex, cigarette consumption, nature of operation and previous history of respiratory disease (*Table I*). Despite strict clinical criteria for diagnosis of respiratory infection and evidence of radiographic abnormality in 72 patients (90 per cent), only 47 patients (59 per cent) had respiratory pathogens identified on sputum culture. The predominant organisms in both groups were *Haemophilus influenzae* and *Streptococcus pneumoniae* (*Table II*).

Table I: COMPARISON OF GROUPS

	Cefuroxime ($n = 41$)	No antibiotic ($n = 39$)
Fever more than 38 °C	39 (95%)	37 (95%)
Purulent sputum	41 (100%)	37 (92%)
Radiographic signs	37 (90%)	35 (90%)
Mean age (yr)	49	47
Male	10 (25%)	11 (28%)
More than 20 cigarettes per day	20 (49%)	13 (33%)
Previous chronic respiratory disease	7 (17%)	6 (15%)
Operation		
Gastric	26	22
Biliary	3	8
Colorectal	6	4
Others	5	3

Table II: MICRO-ORGANISMS ISOLATED FROM SPUTUM

	Cefuroxime	No antibiotic
26 *Haemophilus influenzae*	16	10
24 *Streptococcus pneumoniae*	10	14
2 *Klebsiella aerogenes*	—	2
2 *Klebsiella pneumoniae*	1	1
5 *Escherichia coli*	1	4
2 *Proteus* spp.	2	1
3 *Pseudomonas aeruginosa*	3	—
7 *Staphylococcus aureus*	4	3

The numbers of patients with persisting pyrexia after 3 and 5 days were similar in both groups. Radiographic changes were still present at the end of therapy (5 days) in 38 per cent of the treated group

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* The General Hospital, Birmingham.

Table III: RESULTS OF THE TRIAL

	Cefuroxime		No. antibiotics	
	No.	%	No.	%
Persisting fever				
3 d	37	90	35	90
5 d	9	22	13	33
Persisting radiographic signs				
3 d	27	67	26	67
5 d	15	38	19	48
Persisting infective sputum				
3 d	20	50	31	80
5 d	9	23	13	33
Subjective assessment of response				
Excellent	26	63	22	56
Fair	8	19	9	23
Poor	7	17	8	20

compared with 48 per cent of the controls. The sputum remained infected 5 days after starting treatment in 23 per cent of the antibiotic group compared with 33 per cent of the controls. A subjective assessment of response to therapy indicated that the clinical response was similar in both groups (*Table III*).

The results were also analysed in the 13 patients with severe pre-existing respiratory sepsis. Persistent fever was recorded at the end of treatment in 2 of the 7 patients receiving cefuroxime compared with 1 of the 6 controls. Persistent infected sputum at 5 days was also recorded in 2 of the 7 treated patients compared with 2 of the 6 controls.

Additional antibiotic therapy was used in 8 patients because of failure to respond to the trial regimen; 3 were patients receiving cefuroxime, the remaining 5 patients were in the control group. Three patients in the trial died; in 2 death was due to advanced malignancy but 1 patient not receiving antibiotics developed overwhelming respiratory failure requiring ventilation and died despite subsequent antibiotic therapy.

All of the respiratory isolates with the exception of *Pseudomonas aeruginosa* and one strain of *P. mirabilis* were sensitive to 30 mg discs of cefuroxime. The concentration of cefuroxime in the sputum in patients receiving therapy ranged from 0 to 4·7 μg/ml (mean 0·74 μg/ml).

Discussion

This trial has indicated that most patients who develop respiratory complications after abdominal operations respond satisfactorily to physiotherapy alone. The addition of cefuroxime, an antibiotic shown to be effective against almost all respiratory pathogens, rarely gave any additional benefit to patients. However, the general trend of these results suggests that the patients receiving cefuroxime fared slightly better than the controls, even though statistical analysis failed to demonstrate any significant advantage in the antibiotic group. Analysis of the results, even amongst patients with severe pre-existing respiratory infection, in whom prophylactic antibiotics would normally be advised (Dudley et al., 1962), showed that patients receiving antibiotics did not appear to show any improvement over those treated with physiotherapy alone.

With the exception of *P. aeruginosa* and *Proteus* spp., all other respiratory isolates were sensitive to cefuroxime. Even after 5 days' treatment, however, 5 patients still had sensitive bacteria isolated from the sputum. Cefuroxime levels in sputum rarely exceeded the minimal inhibitory concentration for most respiratory pathogens, which is in accordance with the results of other studies (Pines et al., 1977). These results suggest, therefore, that systemic therapy may not always be appropriate in patients with postoperative respiratory sepsis.

Although there were no drug-induced complications with cefuroxime, a course of injections lasting 5 days was frequently reported by patients to be painful. For this reason we would not recommend antibiotics routinely for established postoperative respiratory sepsis since improvement can be expected with physiotherapy alone in most patients.

It could be argued that with greater numbers a significant difference between the groups might have been achieved. An earlier analysis of the results suggested that cefuroxime might prove to be effective therapy, but at that stage the groups were poorly matched for age and type of operation (Keighley and Litchfield, 1978). It was felt that a total of 80 patients would probably demonstrate an important difference if one was present. The analysis of the present data does not support the earlier findings and indicates that antibiotics have little place in the management of postoperative chest infection.

There is also very little evidence that preoperative prophylactic antibiotics reduce the incidence of postoperative respiratory sepsis (Laszlo et al., 1973; Presley and Alexander-Williams, 1974). Furthermore, this study and others indicate that respiratory complications are frequently transient and respond to physiotherapy (Collins et al., 1968) and that many patients with postoperative respiratory complications have atelectasis without bacterial infection in the sputum. Because of the dangers of unnecessary antibiotic therapy (Garrod, 1972), we would not recommend routine prophylaxis for all patients and would advise that antibiotic prophylaxis be reserved for patients with pre-existing respiratory sepsis or cardiorespiratory failure.

References

BRITISH MEDICAL JOURNAL (1977) Postoperative chest infections. **2**, 1500–1501.

CAHILL J. M. (1968) Respiratory problems in surgery patients. *Am. J. Surg.* **116**, 362–368.

CAVANAGH P., KATTAN S. and SYKES R. B. (1976) Antibiotic sensitivity to haemophilus influenza. In: WILLIAMS J. D. and GEDDES A. M. (ed.) *Chemotherapy*, vol. 3. New York, Plenum Press, pp. 247–249.

COLLINS C. D., DARKE C. S. and KNOWELDEN F. (1968) Chest complications after upper abdominal surgery, their anticipation and prevention. *Br. Med. J.* **1**, 401–406.

DUDLEY H. A. F., BAKER W. W. and ANDERSON W. A. (1962) The place of bronchoscopy and tracheostomy in general surgical patients. *J. R. Coll. Surg. Edinb.* 7, 121–127.

GARROD L. P. (1972) Causes of failure in antibiotic treatment. *Br. Med. J.* **4**, 473–476.

GOMME L. (1977) Cefuroxime treatment of patients with lower respiratory and urinary tract infections. *Proc. R. Soc. Med.* **70**, Suppl. 9, pp. 82–85.

HOWARD A. J., HINCE C. J. and WILLIAMS J. D. (1978) Antibiotic resistance in *Streptococcus pneumoniae* and *Haemophilus influenzae*: report of a study group on bacterial resistance. *Br. Med. J.* **1**, 1657–1659.

KEIGHLEY M. R. B. and LITCHFIELD J. C. (1978) A controlled trial of cefuroxime in the management of established postoperative respiratory infections. The early evaluation of cefuroxime. Greenford, Middlesex, Glaxo Research Ltd, pp. 153–158.

LASZLO G., ARCHER G. G., DARREL[illegible] J. H. et al. (1973) The diagnosis and prophylaxis of pulmonary complications of surgical operation. *Br. J. Surg.* **60**, 129–134.

MUNRO D. D. (1970) Practical guides to prophylaxis and treatment of lung complications. *Surgery* **66**, 727–728.

O'CALLAGHAN C. H., SYKES R. B., GRIFFITHS A. et al. (1976) Cefuroxime—a new cephalosporin antibiotic: activity *in vitro*. *Antimicrob. Chemother.* **9**, 511–519.

PINES A., RAAFAT H., TAYLOR-PEARCE M. et al. (1977) Cefuroxime in lower respiratory infections—a preliminary communication. The early evaluation of cefuroxime. Greenford, Middlesex, Glaxo Research Ltd, pp. 95–101.

PRESLEY A. P. and ALEXANDER-WILLIAMS J. (197[illegible]) [illegible]operative chest infection. *Br. J. Surg.* **61**, 448–452.

WEIGH[illegible]AN J. A. K. (1968) A prospective survey of the incidence of postoperative pulmonary complications. *Br. J. Surg.* **55**, 86–91.

Paper accepted 11 September 1978.

Some of the important international conferences and meetings of 1979–80

April
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2–5 April 1979: Denver

Association for Thoracic Surgery
30 April–2 May 1979: Boston

May
International College of Surgeons
13–19 May 1979: Paris

American Urological Association
14–17 May 1979: New York

International Confederation for Plastic and Reconstructive Surgery
20–25 May 1979: Saõ Paulo

June
American Society of Colon and Rectal Surgeons
10–14 June 1979: Atlanta

18th Congress of the International Urology Society
24–29 June 1979: Paris

July
6th European Congress of Neurosurgery
16–20 July 1979: Paris

Congress of British Association of Paediatric Surgery
18–21 July 1979: Marseille

September
American Association for Surgery of Trauma
27–29 September 1979: Chicago

October
Congress of Neurological Surgeons
8–12 October 1979: Las Vegas

American College of Gastroenterology
21–27 October 1979: Atlanta

American College of Surgeons
22–26 October 1979: Chicago

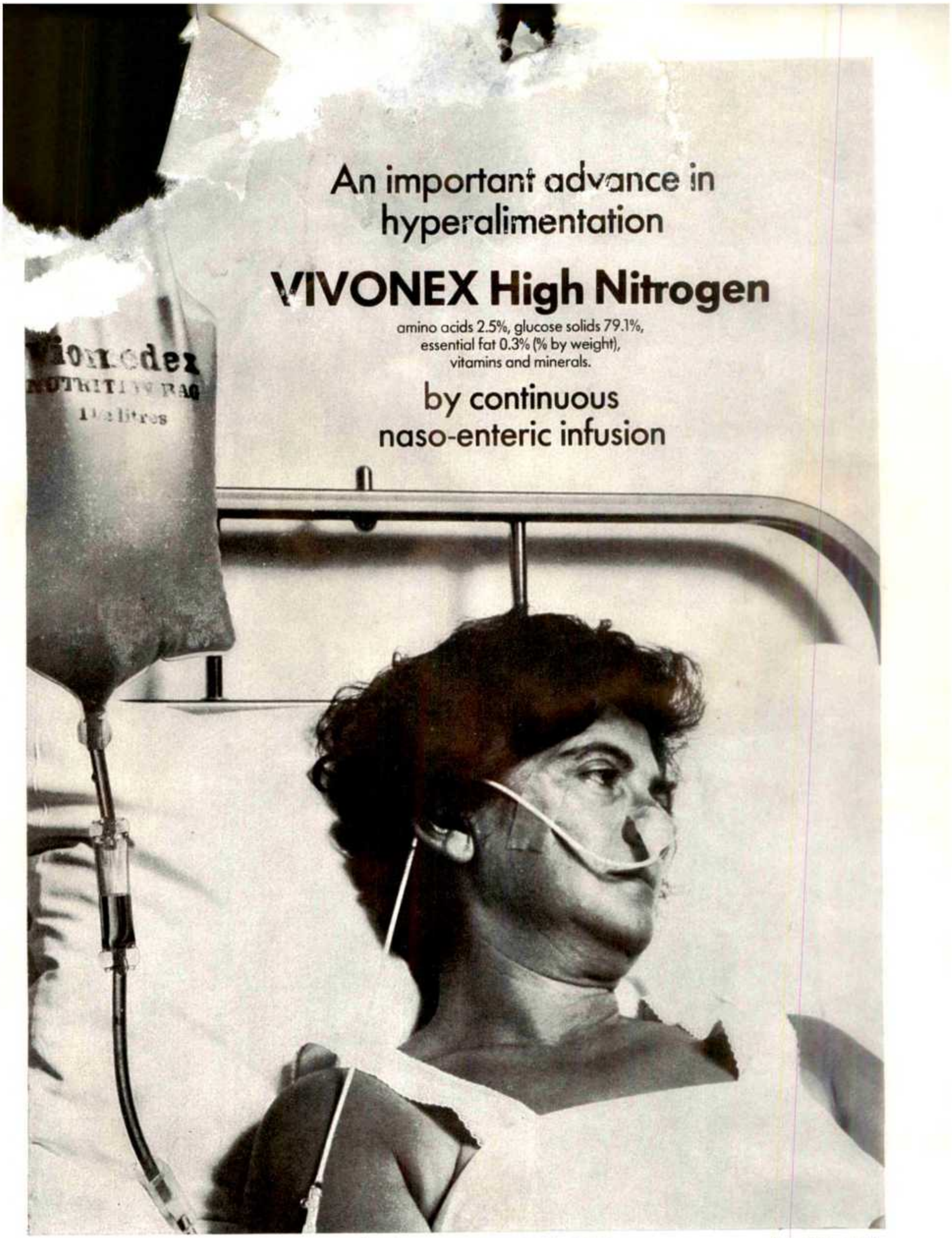
American Cancer Society
5–9 November 1979: New York

February
8th International Thyroid Congress
7–9 February 1980: Melbourne

June
World Congress of Paediatric Cardiology
2–6 June 1980: London

European Congress on Gastroenterology
8–22 June 1980: Hamburg

14th World Congress for Rehabilitation
22–27 June 1980: Winnipeg



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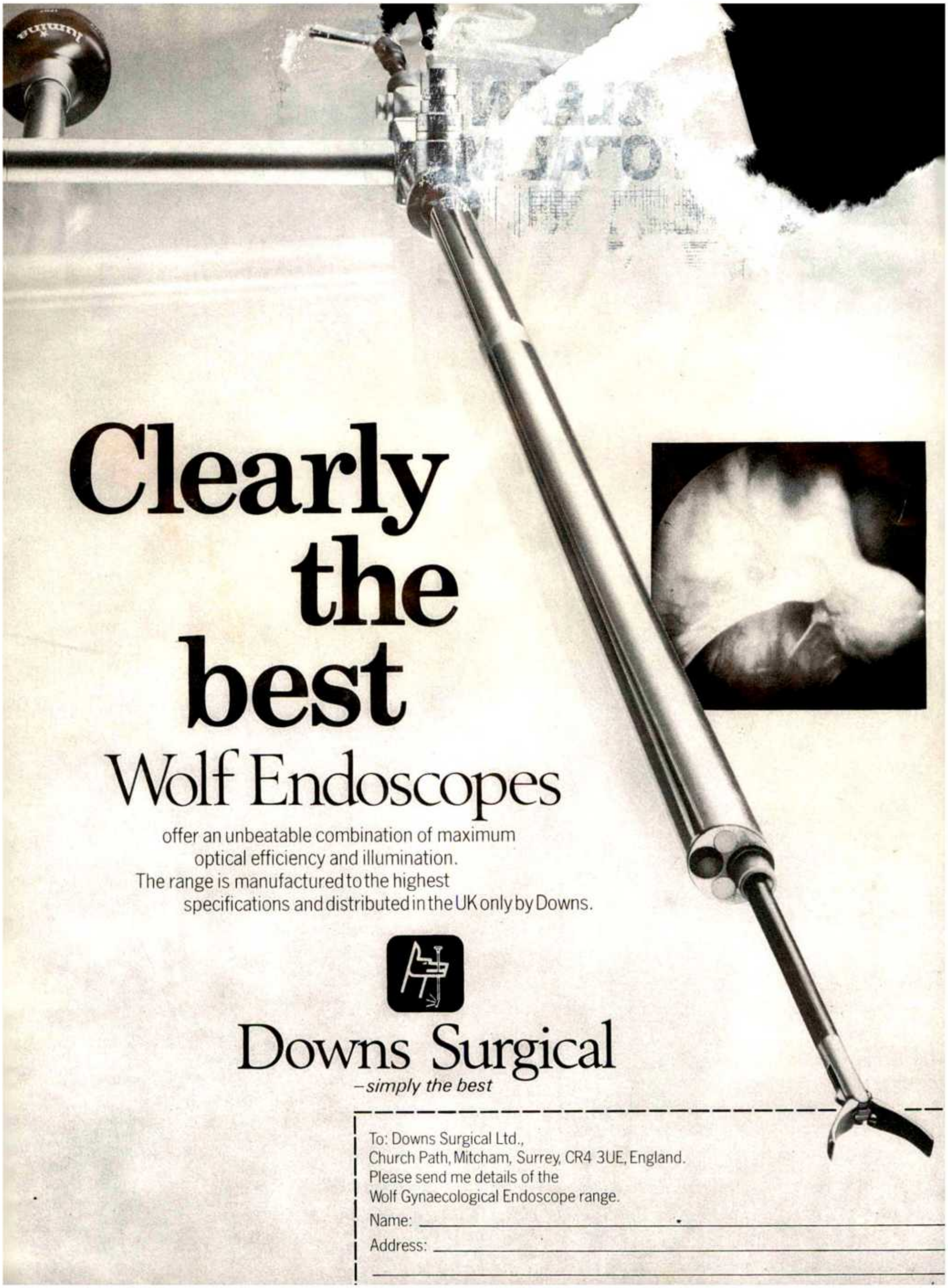

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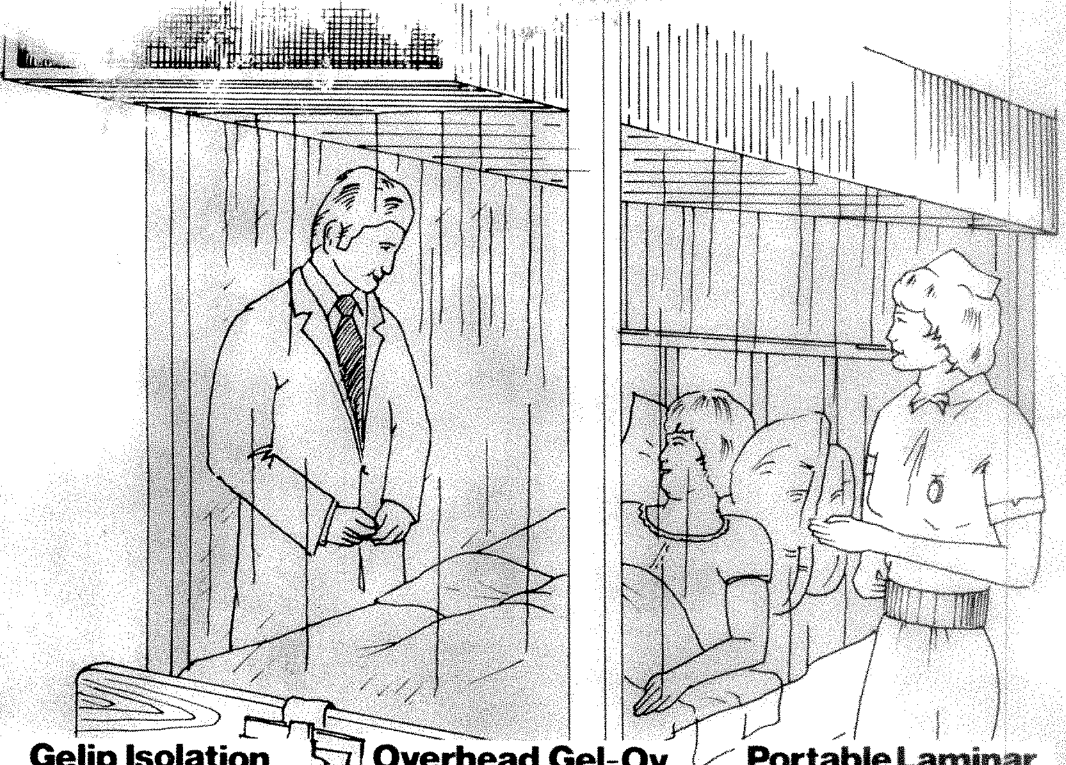

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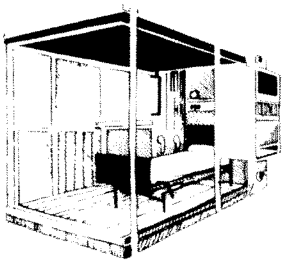

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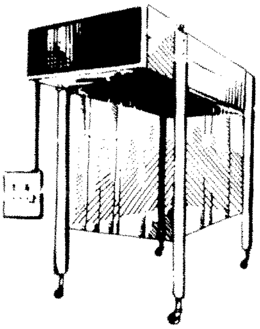

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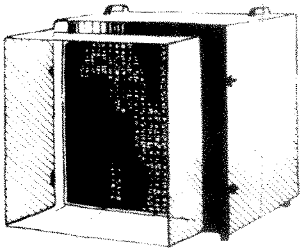

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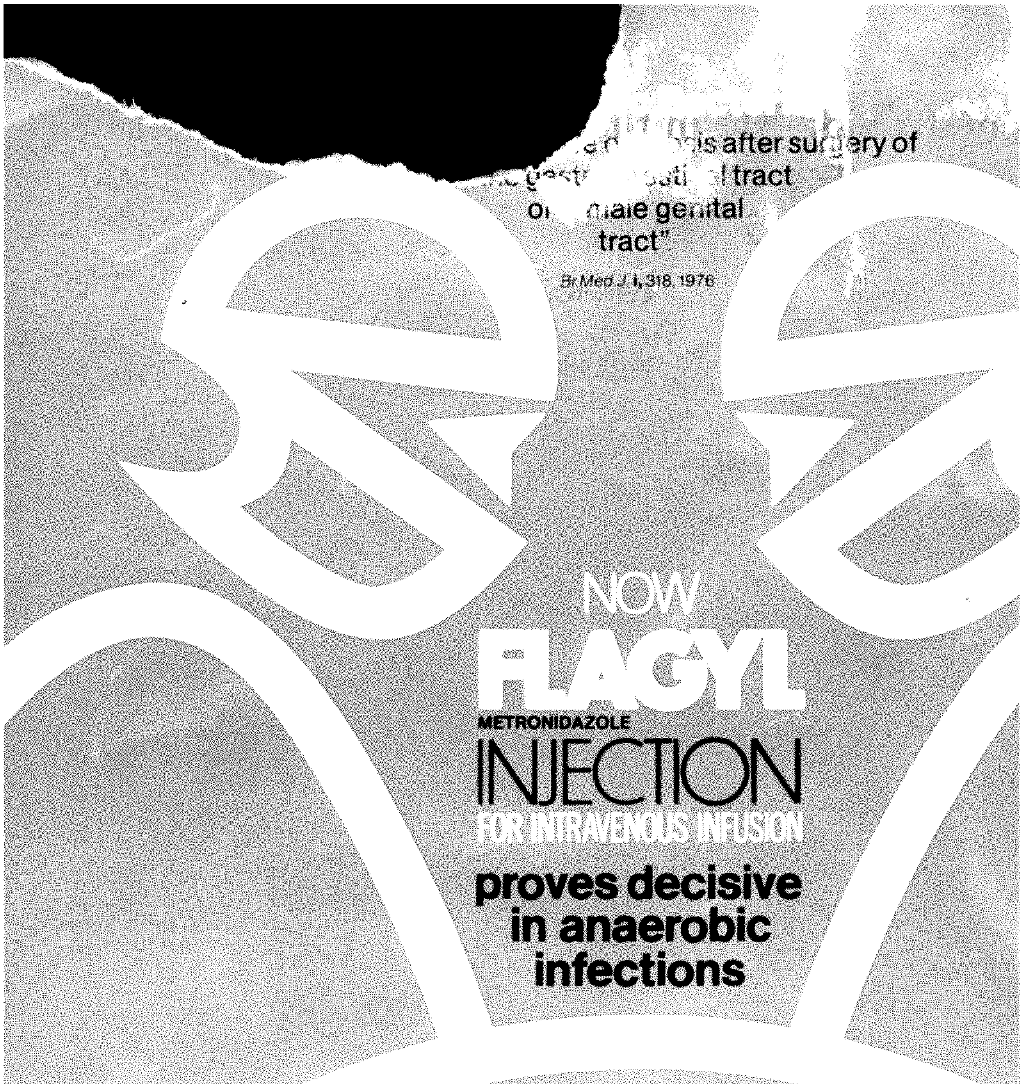

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Br Med J **i**, 318, 1976

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References 1. Willis, A.T. (1977) Scottish Medical Journal, **22**, 155. 2. Willis, A.T. e (1977) British Medical Journal, **i**, 607. 3. Finegold, S.M. Anaerobic Bacteria in Human Disease, Academic Press Inc. New York, 1977. 4. Willis, A.T. et al (1975) Journal of Antimicrobial Chemotherapy, **1**, 393, 1975.

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[illegible] *a.* [illegible] *ne patients receive* [illegible] *alazole and 59 received Thalazo* [illegible] *curred in 8 (13·1 per cent) of the 61 pati* [illegible] *received metronidazole, compared with 29 (49·2 per cent) of 59 patients who received only Thalazole. Of the 8 patients with sepsis who received metronidazole, none had infection due to anaerobic organisms.*

IT has been known for over a decade that nearly 80 per cent of the faecal flora consists of *Bacteroides* species (van Houte and Gibbons, 1966). It is, however, only recently that attention has been drawn to the use of antibiotics with specific action against these anaerobic organisms in the preparation of the bowel for surgery (Willis et al., 1977). Any major advance to be made in the control of postoperative sepsis following bowel surgery would clearly lie in the choice of an antibiotic effective against anaerobic organisms. With this in mind we designed a trial comparing two groups of patients undergoing colonic resection, in which one group received the antibiotic metronidazole, which is strictly effective against anaerobic organisms. The preliminary results (Taylor and Cawdery, 1977) indicated that a reduction in the wound sepsis rate could be achieved using such an antibiotic. The decision whether to give the control group an antibiotic or not was difficult. Recent observations (*British Medical Journal*, 1976) have suggested that all that is required for adequate bowel preparation is mechanical cleaning. When we planned the study, however, we relied upon the earlier observations of Rosenberg et al. (1971), which indicated that mechanical cleaning alone was inferior to the addition of Thalazole to the regimen. We accordingly used Thalazole to minimize the risk to our patients.

Patients and methods

Patients in whom colonic resection was planned were randomized into two groups by a secretary who selected an appropriately labelled card. Patients in group A received oral Thalazole 2·5 g four times a day for 4 days, while those in group B received oral metronidazole 400 mg three times a day for 4 days in addition to Thalazole in the same dosage, i.e. 2·5 g four times a day. In both groups the bowel was prepared mechanically in an identical way and an oral elemental diet was given during the 4 days of preparation, so that only the antibiotic treatment varied. Antibiotic cover was not extended into the postoperative period. After operation the wound was inspected at intervals determined by the surgical team in charge of the patient and any inflammation or sepsis was recorded using the criteria of Ljungqvist (1964) and a bacteriological swab was taken for aerobic and anaerobic culture. Twenty patients from each group were studied for change in faecal flora by taking a bacteriological swab from the lumen of the specimen after resection and setting it up for aerobic and anaerobic culture.

In all, 126 patients were allocated to the trial. There were 6 exclusions—4 from group A and 2 from group B—for reasons of inoperability or the use of a systemic antibiotic in the early postoperative period. The age range of the group A patients [illegible]s 26–80 years (mean 60) and that of 34–79 years (mean 57). There were 2 patients in group A and 20 male and group B.

Statistical analysis was performed usi paired alternatives.

Results

Results of faecal sampling

The results from 40 patients (20 show that the incidence of anae group B patients was significantly with group A patients. Only 2 p grew anaerobes from the faecal sa patients from group A. The ana in group B patients were clostridi less sensitive to metronidazole th organisms.

Postoperative sepsis

Of the 120 patients eligible for st group A and 61 from group B. 49·2 per cent in group A and 13· is a significant reduction in sepsis Perineal sepsis occurred more fre patients (10 out of 15 *v*. 6 out of 1 was not statistically significant patients in group A who had a the rectum showed a much higher sepsis than those in group B (*Ta* *v*. 2 out of 31) and the difference 0·001).

Table I: POSTOPERATIVE SEPSIS AFTER COLONIC SURGERY

Operation	Group A	N w se
Abdominoperineal excision	15	l
Anterior resection	30	l
Right hemicolectomy	9	
Other, e.g. polypectomy, laparotomy, appendicectomy	5	
Exclusions	2	
Total	61	2 (49

The organisms cultured from i each group are listed in *Table I* were isolated from 17 infected w and from no wounds in group B wound infections caused by an tended to be affected constitutiona by way of a rise in temperature Those patients with an aerobic

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* Departments of Surgery and Microb Hospital, London, and the Royal Sus Brighton.

Clostridia	5	[illegible]
Staphylococcus aureus	7	4
Streptococcus faecalis	0	2

(*Escherichia coli*, *Streptococcus faecalis* and *Staphylococcus aureus*) tended to be less ill and the wound discharge was noted to be less copious and less offensive.

Two patients from each group sustained deep pelvic infection following anterior resection of the rectum with discharge of pus from the drain site and per rectum. All had associated infection of the abdominal wound. Two group A patients had septicaemic episodes in the postoperative period. In one a *Bacteroides* sp. was grown on blood culture and treatment with metronidazole was effective. The infection appeared to arise from coexistent pelvic and wound infections.

Discussion

There is evidence that the addition of metronidazole to a standard bowel preparation reduces the rate of wound sepsis after operation. It is also evident that the drug is effective in eliminating infection due to anaerobic organisms. (*Table II.*) In group A there were 17 instances of infection due to *Bacteroides* spp. and none in group B patients ($P < 0{\cdot}001$). It also seems that prophylaxis with the drug is only required during the preoperative preparation of the patient for the elimination of infection due to anaerobic organisms. Its use therefore need not be extended into the postoperative period. Metronidazole is entirely selective in its effects on anaerobic organisms and is completely inactive against aerobic bacteria (Willis et al., 1977). It appears to be non-toxic when used for short periods and at low total dosage. The results obtained in our series suggest that in some way anaerobic organisms work in synergism with aerobic organisms to produce their effects in the wound. Removal of the anaerobes alone may be all that is required to reduce sepsis and it may be unnecessary to add another antibiotic effective against Gram-negative bacteria (Goldring et al., 1975). Recent information supporting this hypothesis comes from Ingham et al. (1977), who provide evidence that *Bacteroides melaninogenicus* and *B. fragilis* interfere with the phagocytosis and killing of *P. mirabilis* and other aerobic bacteria *in vitro*, thus rendering them pathogenic. This could explain why agents such as Thalazole used alone, as in our control group, are

o[illegible]
wh[illegible]
tive [illegible] note that in group B pa[illegible]
it was [illegible] und which became infected and not the [illegible] ominal incision, whereas those patients in group A who developed perineal wound infection also had infected abdominal wounds.

These results are an improvement on those of other quoted series in which lincomycin was given (Downing et al., 1977). The use of improved methods of cleansing the bowel by mechanical means is now well established (Crapp et al., 1975). This, in conjunction with meticulous surgical technique and the elimination of anaerobic organisms from the resected colon, serves to improve the sepsis rate after colonic surgery.

Acknowledgement

We are grateful to the surgeons of King's College Hospital, London, and the Brighton Hospitals for allowing us to study their patients.

References

BRITISH MEDICAL JOURNAL (1976) **2**, 773.

CRAPP A. R., POWIS S. J. A., TILLOTSON P. et al. (1975) Preparation of the bowel by whole-gut irrigation. *Lancet* **2**, 1239–1240.

DOWNING R., MCLEISH A. R., BUROON D. W. et al. (1977) Duration of systemic prophylactic antibiotic cover against anaerobic sepsis in intestinal surgery. *Dis. Colon Rectum* **20**, 401–404.

GOLDRING J., SCOTT A., MCNAUGHT W. et al. (1975) Prophylactic oral antimicrobial agents in elective colonic surgery. *Lancet* **2**, 997–999.

INGHAM H. R., SISSON P. R., THARAGONNET D. et al. (1977) Inhibition of phagocytosis *in vitro* by obligate anaerobes. *Lancet* **2**, 1252–1254.

LJUNGQVIST U. (1964) Wound sepsis after clean operations. *Lancet* **1**, 1095–1097.

ROSENBERG I. L., GRAHAM N. G., DE DOMBAL F. T. et al. (1971) Preparation of the intestine in patients undergoing major large-bowel surgery, mainly for neoplasms of the colon and rectum. *Br. J. Surg.* **58**, 266–269.

TAYLOR S. A. and CAWDERY H. M. (1977) The use of metronidazole in the preparation of the bowel for surgery. *Proc. R. Soc. Med.* **70**, 481–482.

VAN HOUTE J. and GIBBONS R. J. (1966) Studies of the cultivable flora of normal human faeces. *Antonie van Leeuwenhoek* **32**, 212–222.

WILLIS A. T., FERGUSON I. R., JONES P. H. et al. (1977) Metronidazole in prevention and treatment of *Bacteroides* infections in elective colonic surgery. *Br. Med. J.* **1**, 607–610.

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One-dose antibiotic prophylaxis against wound infection after appendicectomy: a randomized trial of clindamycin, cefazolin sodium and a placebo

I. A. DONOVAN, D. ELLIS, D. GATEHOUSE, G. LITTLE,
R. GRIMLEY, S. ARMISTEAD, M. R. B. KEIGHLEY AND C. J. L. STRACHAN*

SUMMARY

Two hundred and fifty patients were admitted to a prospective randomized trial of single dosage prophylaxis against wound infection after appendicectomy. There were 12 exclusions, 72 patients received placebo, 81 received 600 mg i.m. clindamycin phosphate and 85 received 1 g i.m. cefazolin sodium, the agent being given in the anaesthetic room. Clindamycin produced a significant reduction in the overall rate of wound infection from 33 per cent in the controls to 17 per cent. In cases with a gangrenous or perforated appendix the infection rate in controls was 78 per cent; this was reduced to 44 per cent by a single dose of clindamycin.

Cefazolin significantly reduced the number of aerobic organisms isolated from wound infections, but did not significantly reduce the incidence of wound infection. We conclude that anaerobic organisms are more important than faecal aerobic organisms in the pathogenesis of wound infection after appendicectomy.

WOUND infection has been reported to occur in up to 30 per cent of all patients after appendicectomy (Bird et al., 1971), and the incidence may be as high as 63 per cent in perforated appendicitis (Leigh et al., 1974).

Leigh and his colleagues (1974) found bacteroides in 78 per cent of their isolates from swabs of the appendix fossa taken at appendicectomy. One of the most active antibiotics against bacteroides is clindamycin (Kislak, 1972; Sutter, 1977), which became available in parenteral form as clindamycin phosphate in Great Britain in 1976. A prospective trial of clindamycin phosphate was therefore undertaken to determine its efficiency against wound infection after appendicectomy. In the present trial we have compared clindamycin with an antibiotic whose main activity is against the faecal aerobic organisms. Cefazolin sodium has been shown by Strachan and his colleagues (1977) to be a very effective prophylactic against wound infection after cholecystectomy even when given as a single dose, and we therefore decided to use this agent in a similar regimen in cases of appendicitis. From this trial we hoped to determine whether anaerobic or aerobic organisms were the most important in the genesis of post-appendicectomy wound infections.

Patients and methods

A prospective randomized trial of cefazolin sodium, clindamycin phosphate and placebo was established. Randomization was based on a table of random numbers. A single dose was given by intramuscular injection to the anaesthetized patient in the anaesthetic room. The patient received 600 mg of clindamycin phosphate or 1 g of cefazolin sodium or 3 ml of placebo. The phials were identified by a code number. The trial was conducted in several centres, 4 hospitals entering a total of 250 patients into the study. Excluded from entry to the trial were children under the age of 12 years, patients who had received antibiotics within the previous 7 days before operation and patients with a history of penicillin allergy.

In each hospital there was an assessor who inspected the wounds. Wound sepsis was defined as the discharge of pus from the wound either spontaneously or after incision. All patients were given a follow-up appointment for wound inspection by the assessor 2–3 weeks after operation.

A numbered form was provided, the number on the form corresponding with a numbered phial of drug or placebo kept in the theatre refrigerator. The surgeon was asked to record the incision, the presence and nature of intraperitoneal fluid, the macroscopic appearance of the appendix, the use and siting of drains and the use of peritoneal lavage with normal saline. The use of topical antibiotics or antiseptics in the peritoneal cavity or the wound was prohibited.

At operation the appendix was divided and half was sent for histopathology and half was placed in transport medium for microbiology. Emergency microbiology was not feasible. Aerobic and anaerobic cultures of the appendix were prepared during normal working hours. Pus from wound infections was collected and taken immediately to the microbiology laboratory for aerobic and anaerobic culture. Unfortunately, specimens were not usually obtainable from patients whose wounds became purulent after hospital discharge.

The cultures for anaerobic organisms were made on selective media (Rogossa agar and lysed blood agar containing menadione), and were cultured either in an anaerobic chamber or in anaerobic jars for 7 days. The details of the method varied slightly from hospital to hospital.

Results

The trial was opened in December 1976 and closed 12 months later, at which time 250 patients had been admitted. There were 12 withdrawals either due to other pathology being present (7 patients) or due to the addition of antibiotics within 48 h of operation with no subsequent development of wound infection (5 patients).

Of the residual 238 patients, 72 received placebo, 81 received clindamycin and 85 cefazolin. The overall infection rates in the three groups are shown in *Table I*. The statistical test applied throughout in this paper was the χ^2 test with the Yates' correction. There are a number of high risk factors which may produce unfavourable bias in overall figures in appendicitis. The most important of these are the state of the appendix (Leigh et al., 1974), the use of drains (Brumer, 1970) and the age of the patient (Kingsley, 1969).

On the basis of the surgeon's opinion at operation and on histological examination, the appendix was graded as normal, acutely inflamed and perforated or gangrenous. The distribution of these grades in the three trial groups is shown in *Table II*. There was a greater proportion of perforated or gangrenous appendices in the cefazolin group compared with

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* Dudley Road Hospital, The General Hospital and Queen Elizabeth Hospital, Birmingham, and Huddersfield Royal Infirmary.

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Table I: OVERALL WOUND INFE[illegible]ONS IN [illegible]E THREE GROUPS

	Total	Not infected	Infected	%
Placebo	72	48	24	33
Clindamycin	81	67	14	17
Cefazolin	85	55	30	35

Clindamycin *v.* placebo: $\chi^2 = 4{\cdot}4$, $P < 0{\cdot}05$.
Clindamycin *v.* cefazolin: $\chi^2 = 6{\cdot}0$, $P < 0{\cdot}025$.

Table II: STATE OF THE APPENDIX REMOVED

	Normal	Acutely inflamed	Gangrenous or perforated
Placebo	20	43	9
Clindamycin	24	39	18
Cefazolin	18	42	25
Total	62	124	52

Table III: INFECTION RATES IN CASES WITH A GANGRENOUS OR PERFORATED APPENDIX

	Not infected	Infected	%
Placebo	2	7	78
Clindamycin	10	8	44
Cefazolin	5	20	80

Table IV: INFECTION RATES IN CASES WITH A NORMAL OR ACUTELY INFLAMED APPENDIX

	No. normal	Infected No.	Infected %	No. acutely inflamed	Infected No.	Infected %
Placebo	20	4	20	43	13	30
Clindamycin	24	1	4	39	5	13
Cefazolin	18	1	6	42	9	21

Table V: INFECTION RATES IN PATIENTS OVER THE AGE OF 40 WITH REGARD TO THE STATE OF THE APPENDIX

	Normal		Acutely inflamed		Gangrenous	
	No.	Inf.	No.	Inf.	No.	Inf.
Placebo	2	1	8	4	3	3
Clindamycin	3	0	3	1	5	3
Cefazolin	0	0	3	0	7	7

Inf., Infected.

Table VI: THE PRESENCE AND NATURE OF INTRAPERITONEAL FLUID IN RELATION TO THE STATE OF THE APPENDIX

	No fluid (%)	Straw-coloured fluid (%)	Purulent fluid (%)
Normal	87	11	2
Acutely inflamed	50	40	10
Perforated or gangrenous	1	29	70

Table VII: AEROBIC AND ANAEROBIC ISOLATES FROM WOUND INFECTIO[illegible]

	[illegible]	acultative bes
Placebo	[illegible]	[illegible]
Clindamycin	[illegible]	[illegible]
Cefazolin	[illegible]	[illegible]

Table VIII: RESU[illegible] PROPHYLAXIS [illegible] AFTER APPENDICEC[illegible]

Agent	Administration	% treated	% in controls	% reduction
†Ampicillin	Topical	4	17	77
‡Ampicillin	Topical	3	16	81
§Povidone-iodine	Topical	8	16	50
‖Lincomycin	Single dose i.m.	6*	17	65
¶Ampicillin	Topical	3	41	93
**Ampicillin	Topical	3	24	87
††Metronidazole	5 days rectal	10	24	41

* Excluded cases with perforated appendix.
† Andersen et al. (1972). ‡ Bates et al. (1974). § Gilmore and Martin (1974). ‖ Leigh et al. (1976). ¶ Mountain and Seal (1970). ** Rickett and Jackson (1969). †† Willis et al. (1976).

both the clindamycin and the placebo group, the latter having the lowest proportion of all. We have, therefore, examined the rate of wound infection in the gangrenous or perforated group separately (*Table III*). The rates of wound sepsis in the placebo and cefazolin group were virtually identical but that in the clindamycin group was significantly lower ($\chi^2 = 5{\cdot}05$, $P < 0{\cdot}025$).

The incidence of wound sepsis in the normal and acutely inflamed groups is shown in *Table IV*. Despite considerable percentage variation in infection rates, no significant differences were demonstrable on statistical analysis because the numbers in the subgroups are small. However, the distribution of cases is comparable in the three trial groups with regard to normal and acutely inflamed appendices and if these categories are considered together, clindamycin produced a significant reduction in wound infection compared with the placebo ($\chi^2 = 5{\cdot}3$, $P < 0{\cdot}025$); cefazolin produced no significant effect.

Drains were used in 12 of the placebo group, 14 of the clindamycin group and 15 of the cefazolin patients, a total of 41 out of 238 patients. Twelve of these were in cases of acute appendicitis, of whom 3 developed wound infection, all in the placebo group. Of the remaining 29 in the gangrenous or perforated category, 3 of 5 in the placebo, 13 of 14 in the cefazolin and 8 of 10 in the clindamycin group developed wound infections. These numbers are too small to permit any comment other than that the incidence of drainage in cases of gangrenous perforated appendix was 56 per cent in all three trial groups so that there is no evidence of bias.

Table V shows the infection rates in patients over the age of 40 with regard also to the state of the appendix. There is no obvious bias in favour of any group.

There were 5 more severe septic complications; all occurred in patients with a perforated or gangrenous appendix who subsequently developed wound infections. One patient had an ileus lasting for 2 weeks and another had a re-exploration for suspected intra-abdominal pus, although none was found. A third required secondary suture of the wound and a fourth had a pelvic abscess which was drained. One patient died: he was a 74-year-old male chronic bronchitic who had persistent wound and chest infection. He died 3 months after operation of a pulmonary embolism.

Of the 238 patients, 229 had grid-iron incisions and only 9 had right paramedian incisions. No useful analysis was possible on these small numbers and likewise the information on peritoneal lavage with normal [illegible] only 20 patients. The preser[illegible] toneal fluid did not [illegible] elihood of wound [illegible] pparent from the [illegible] frequency of free [illegible] the severity of the [illegible]

[illegible] om the sectioned [illegible] 115 cases, and in [illegible] preparing the cultures, [illegible] for [illegible] as unreliable and are therefore not reporting it. M[illegible]biology was available from 50 of the 68 wound infections. Fifteen (22 per cent) only became manifest after hospital discharge. The incidence of anaerobic and aerobic wound isolates is shown in *Table VII*. Although less anaerobes were grown from infections in the clindamycin group than from the other groups, the difference is not significant, the numbers being too small. There is, however, a significant reduction in the numbers of aerobic isolates from infections in the cefazolin group compared with the others ($\chi^2 = 4{\cdot}6$, $P < 0{\cdot}05$).

Discussion

Previous clinical trials have failed to demonstrate any influence on wound infection when antibiotics are started after operation (McKittrick and Wheelock, 1954; Barnes et al., 1959), and experiments in animals have demonstrated that to provide effective prophylaxis against wound infections the antibiotic must be present in the tissues at the time of operation (Burke, 1961; Alexander-Williams and Altemeier, 1965). We therefore considered that if antibiotics were started more than 48 h after operation, it was unlikely that they would influence development of wound infection, and therefore such patients were not withdrawn from the study. Patients in whom additional antibiotics were started within 48 h of operation were excluded unless they developed a wound infection, in which case the original prophylaxis had failed anyway.

The results of the study show that although an antibiotic active against aerobic organisms was effective in reducing the number of aerobic isolates from wound infections, it had no effect on the incidence of wound infection. An antibiotic effective against anaerobic organisms, however, did significantly reduce wound infections. These findings strongly support the hypothesis that the anaerobic organisms are more important than the facultative aerobes in the production of endogenous wound infection after appendicectomy. The overall reduction in wound infection, however, was not as great as that reported in some other trials, especially those in which topical ampicillin powder has been used (*Table VIII*).

In this trial the wound infection rate in the control group was higher than that in most previously reported series (*Table VIII*), ranging from 20 per cent in the normal patients to 78 per cent in those with gangrenous or perforated appendices. Our finding of 22 per cent of wound infections presenting after hospital discharge is comparable to that of other authors (Gilmore et al., 1973 = 30 per cent; Bates et al., 1974 = 21 per cent). The single dose of clindamycin reduced the incidence of wound infection after removal of a normal appendix from 20 to 4 per cent, providing adequate prophylaxis, and in this group of patients cefazolin also appears to be effective, as the infe[illegible] rate [illegible] only 6 per cent, although the numbers are too small for a statistical comparison.

In acute appendicitis the wound infection rate was reduced from 30 to 13 per cent by clindamycin, no systemic complications of sepsis being seen in any of the three trial groups in acute appendicitis. In cases with gangrenous or perforated appendices the control infection rate of 78 per cent was reduced to the still unacceptably high level of 44 per cent, and more severe complications were seen. In these patients more prolonged antibiotic therapy with clindamycin is required, and it could be argued that systemic cephazolin should also be administered in view of its effect on the aerobic flora, the drug first being given at operation when the severity of the appendicitis has become apparent. In this study the incidence of wound infection in cases described as having gangrenous appendicitis was comparable to the incidence in those cases described as having perforated appendicitis (overall infection rates: gangrenous, 64 per cent; perforated, 70 per cent). We feel justified, therefore, in putting them together as one high risk group.

A single-dose systemic prophylactic regimen, as described here with clindamycin, should produce little risk of the emergence of resistant strains, and is very unlikely to induce pseudomembranous colitis, which is more common when an anti-anaerobic agent is used for longer and in combination with an anti-aerobic agent (Kappas et al., 1978). In this study no cases of pseudomembranous colitis were seen. Three patients developed postoperative diarrhoea and were examined by sigmoidoscopy, but no abnormality was found on biopsy. Two of these patients had received clindamycin and one cephazolin as a single-dose prophylaxis.

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References

ALEXANDER WILLIAMS J. and ALTEMEIER W. A. (1965) Penicillin prophylaxis of experimental staphylococcal wound infections. *Surg. Gynecol. Obstet.* **120**, 243–254.

ANDERSEN B., BENDTSEN A., HOLBRAAD L. et al. (1972) Wound infection after appendicectomy. I. A controlled trial on the prophylactic efficacy of topical ampicillin in non-perforated appendicitis. II. A controlled trial on the prophylactic efficacy of delayed primary suture and topical ampicillin in perforated appendicitis. *Acta Chir. Scand.* **138**, 531–536.

BARNES J., PACE W. G., TRUMP D. S. et al. (1959) Prophylactic postoperative antibiotics: a controlled study of 1007 cases. *Arch. Surg.* **79**, 190–196.

BATES T., DOWN R. H. L., HOUGHTON M. C. V. et al. (1974) Topical ampicillin in the prevention of wound infection after appendicectomy. *Br. J. Surg.* **61**, 489–492.

BIRD G. C., BUNCH G. A., HOFFMANN D. C. et al. (1971) Topical noxythiolin antisepsis: a report of a controlled trial. *Br. J. Surg.* **58**, 447–448.

BRUMER M. (1970) Appendicitis. Seasonal incidence and postoperative wound infection. *Br. J. Surg.* **57**, 93–99.

BURKE J. F. (1961) The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery* **50**, 161–168.

GILMORE O. J. A. and MARTIN T. D. [illegible]4) Aetiology and prevention of wound infection in appendicectomy. *Br. J. Surg.* **61**, 281–287.

GILMORE O. J. A., MARTIN T. D. M. and FLETCHER B. N. (1973) Prevention of wound infection after appendicectomy. *Lancet* **1**, 220–222.

KAPPAS A., SHINAGAWA N., ARABI Y. et al. (1978) Diagnosis [illegible] pseudomembranous colitis. *Br. Med. J.* **1**, 675–678.

KINGSLEY P. P. E. (1969) Some observations on appen[illegible]tomy with particular reference to technique. *Br. J.* [illegible] **56**, 491–496.

KISLAK J. W. (1972) The susceptibility of *Bacteroides fragilis* to 24 antibiotics. *J. Infect. Dis.* **125**, 295–299.

LEIGH D. A., PEASE R., HENDERSEN H. et al. (1976) Prophylactic lincomycin in the prevention of wound infection following appendicectomy: a double blind study. *Br. J. Surg.* **63**, 973–977.

LEIGH D. A., SIMMONS K. and NORRIS E. (1974) Bacterial flora of the appendix fossa in appendicitis and postoperative wound infection. *J. Clin. Pathol.* **27**, 997–1000.

MCKITTRICK L. S. [illegible] (1954) The routine use of antibiotic[illegible]rgery. *Surg. Gynecol. Ob*[illegible]

MO[illegible]cal ampicillin in grid [illegible] *J. Clin. Pract.* **24**, [illegible]

[illegible]69) Topical ampicillin in [illegible] of a double blind trial.

[illegible] S. J. A. et al. (1977) Prophy[illegible] cep[illegible] against wound sepsis after chole[illegible]tomy. *Br. Med. J.* [illegible], 1254–1256.

SUTT[illegible] V. L. (1977) *In vitro* susceptibility of anaerobes: comparison of clindamycin and other antimicrobial agents. *J. Infect. Dis.* [illegible]5, Suppl., pp. 7–12.

WILLIS A. T., FERGUSON I. R., JONES P. H. et al. (1976) Metronidazole in prevention and treatment of bacteroides infections after appendicectomy. *Br. Med. J.* **1**, 318–321.

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Preventi[illegible] eal adhesions: a comparison of noxythi[illegible] vidone-iodine/PVP solution

O. J. A. GILMO[illegible]

SUMMARY

Peritoneal adhesions were induced in 250 [illegible] rats by the excision and closure of a right lower quadrant parietal peritoneal defect. After closure of the defect each rat was randomly allocated to one of five treatment groups: A, control with no instillate; B, control with Ringer solution; C, noxythiolin 0·5 per cent solution; D, noxythiolin 1 per cent solution; E povidone-iodine/PVP solution. Two millilitres of the appropriate solution were injected into the peritoneal cavity just before closure of a standard 4-cm midline incision. Assessment of adhesion formation was made at 1 week in ignorance of the treatment group. Noxythiolin 1 per cent was more effective than Ringer solution and noxythiolin 0·5 per cent in reducing the mean number of adhesions ($P<0\cdot05$) but was inferior to povidone-iodine/PVP ($P<0\cdot05$). Povidone-iodine/PVP solution significantly reduced the number of adhesions compared with the four other groups. In addition, it significantly reduced the mean length of attachment of each adhesion compared with the two control groups ($P<0\cdot001$).

SINCE the advent of abdominal surgery one of the main aims of the surgeon has been to prevent intraperitoneal adhesions. All surgeons dislike finding adhesions when they explore a patient who has had a previous laparotomy. Ellis (1974) reported a 92 per cent incidence of adhesions in such patients. Abdominal surgery is now so common that the adhesions that it produces are the most frequent cause of small bowel obstruction (Ellis, 1974). Krook (1947) concluded from an extensive study that just under 1 per cent of patients who undergo gynaecological surgery develop intestinal obstruction caused by adhesions: this compares with a figure of 4 per cent for those who have an appendicectomy for a perforated appendix.

Ellis (1962, 1971, 1974) believes the aetiology of adhesions to be ischaemic, whereas Boys (1942) and Krook (1947) indicate infection. Experimental and clinical observations suggest that both are potent causes, but whether infection induces adhesions by means of ischaemia remains uncertain.

Noxythiolin (Noxyflex) is a widely used antiseptic and will significantly reduce adhesion formation in the rat (Gilmore and Reid, 1976). A polyvinylpyrrolidone (povidone/PVP) iodine solution containing 1 per cent PVP and 0·1 per cent available iodine failed to prevent adhesions in rats following colectomy (Gilmore, Rosin et al., 1978). However, 6–7 per cent PVP solutions have been effective in both animals (Kalligianis, 1961; Mazuji et al., 1964; Badowski and Daciewicz, 1971) and man (Oetell et al., 1954; Upplegger, 1956). Recently a newly formulated povidone-iodine/PVP solution containing 11 per cent PVP and 0·1 per cent available iodine has been found to reduce significantly peritoneal adhesion formation in the rat (Gilmore and Reid, 1978).

A safe and effective intraperitoneal antiseptic with anti-adhesive properties has enormous potential in elective and emergency surgery. It was therefore decided to compare the efficacy of noxythiolin and povidone-iodine/PVP in preventing adhesions in a standard animal model (Gilmore and Reid, 1976).

Materials and methods

Povidone-iodine/PVP solution

A mixture of 10 g of dry PVP powder and 1 g of dry povidone-iodine (containing 0·9 g PVP and 0·1 g available iodine) was added to approximately 89 g of sterile water. In order to determine the available iodine content (0·1 per cent was required), the solution was titrated against sodium thiosulphate. More sterile water was added and further titrations performed until the povidone-iodine/PVP solution was demonstrated to contain 0·1 per cent available iodine.

Experimental model

A total of 250 female Wistar rats weighing 150–200 g was used. To avoid the chance deposition of starch granules in the peritoneal cavity all the operations were performed without gloves in clean, but not sterile, conditions.

Peritoneal adhesions were induced by the excision and closure of a standard-size peritoneal defect (Gilmore and Reid, 1976). Under ether anaesthesia, following shaving and skin disinfection, the abdomen of each rat was opened through a 4-cm vertical, midline incision.

An area of parietal peritoneum in the right lower quadrant was then grasped and lifted with a pair of Duval forceps measuring 1·4 cm along their grasping tip. The forceps were adjusted so that the flap of peritoneum reached a point 0·5 cm proximal to the teeth of the forceps. The peritoneum and underlying muscle were incised with a scalpel along all margins of the forceps which, when removed, left a clearly marked window of peritoneum measuring 1·0 × 1·4 cm. This window and the underlying muscle were then excised and the resultant defect closed with continuous atraumatic 3/0 black silk sutures.

All abdominal incisions were closed in two layers. The musculoperitoneal layer was closed with continuous 2/0 chromic catgut and the skin was sutured with continuous 2/0 black silk.

A card was drawn allocating each rat to one of five treatment groups: group A, control, no intraperitoneal instillate; group B, control, 2 ml of Ringer solution; group C, 2 ml noxythiolin 0·5 per cent solution; group D, 2 ml noxythiolin 1·0 per cent solution; group E, 2 ml povidone-iodine/PVP solution. All solutions were injected into the peritoneal cavity just before the insertion and tying of the final musculoperitoneal suture.

Assessment of adhesion formation

All rats were killed at 1 week and an autopsy examination of the abdomen performed in ignorance of the treatment group. A reversed 'C' incision was made along the left side of the abdomen, as the peritoneal defect was on the right. In every rat the following details were recorded: number of adhesions present; length of attachment of each adhesion, measured in millimetres with a ruler; the site of origin of each adhesion and the site of adherence.

Statistical methods

The mean number of adhesions per rat was calculated for each treatment group. These means were then compared using the technique of analysis of variance, since five groups were involved (Armitage, 1973). Distribution curves were drawn for

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Table I: TOTAL AND MEAN NUMBER [illegible] ADHESIONS RELATED TO TREATMEN[illegible]

Group	No. of adhesions*	Mean no. adhesions per rat
A	78	1·58
B	92	1·84
C	93	1·88
D	75	1·50
E	59	1·16

* Data for 50 rats.
Standard error of differences in means = 0·016.
E *v*. D, $P<0\cdot05$; E *v*. C, $P<0\cdot001$; E *v*. B, $P<0\cdot001$; E *v*. A, $P<0\cdot001$.
D *v*. C, $P<0\cdot05$; D *v*. B, $P<0\cdot05$; D *v*. A, n.s.

Table II: TOTAL AND MEAN LENGTH OF ATTACHMENT OF ADHESIONS RELATED TO TREATMENT

Group	Length of adhesions* (mm)	Mean length of adhesions per rat (mm)
A	664	8·57
B	736	8·80
C	615	7·30
D	568	6·32
E	345	4·91

* Data for 50 rats.
Standard error of differences in means = 0·819.
E *v*. D, n.s.; E *v*. C, $P<0\cdot01$; E *v*. B, $P<0\cdot001$; E *v*. A, $P<0\cdot001$.
D *v*. C, n.s.; D *v*. B, $P<0\cdot01$; D *v*. A, $P<0\cdot01$.

each treatment group to check that the data were normally distributed. An overall F test of the treatment effects was carried out before comparison of individual pairs of means by an unpaired Student's t test (Armitage, 1973). This gave protection against spurious significant differences arising from the simultaneous comparison of several means.

The average length of adhesions was calculated for each rat. The means for each treatment group were again compared by analysis of variance.

Results

The peroperative intraperitoneal instillation of povidone-iodine/PVP solution gave a statistically significant reduction in the number of adhesions formed in treated rats, compared with all four other groups (*Table I*). Treatment with the povidone-iodine/PVP solution not only resulted in fewer adhesions, but the mean length of attachment of each adhesion was significantly shorter than for either of the two control groups or for group C (*Table II*).

The rats treated with noxythiolin 1 per cent had significantly fewer adhesions ($P<0\cdot05$) compared with groups B and C (*Table I*). The mean length of attachment of each of these adhesions was significantly shorter than that of those occurring in either of the control groups ($P<0\cdot01$) (*Table II*).

Of the 250 rats in the study, 229 developed adhesions. Of the 21 who had no adhesions, 12 were in group E (povidone-iodine/PVP solution) and 8 in group D (noxythiolin 1 per cent). The intraperitoneal instillation of Ringer solution or noxythiolin 0·5 per cent had no effect on the incidence of adhesion formation (*Tables I, II*).

The mean total length of attachment of adhesions per rat (as opposed to the mean length of each adhesion) varied according to the treatment group. Rats in group A had an average 13·3 mm of adhesions, those in group B 14·7 mm, group C 12·3 mm, group D 11·4 mm and group E 6·9 mm.

Throughout the study, all the adhesions seen were either adherent to the peritoneal defect or to the midline abdominal wound. Rats treated with povidone-iodine/PVP solution had fewer adhesions to both sites. Seventy-one rats (28·4 per cent) in the study developed adhesions to the midline laparotomy scar. The incidence of adhesions to this site varied from 14 per cent in the povidone-iodine/PVP group to 46 per cent in the noxythiolin 0·5 per cent group.

The commonest structure found at autopsy to be adherent to either the peritoneal defect or the midline scar was the ovarian complex. The ovary in the rat lies at the end of a long Fallopian tube which has attached to it an abundant broad ligament or mesentery. The entire complex is mobile. The greater omentum was the next most frequently involved with adhesions. Both the broad ligament (mesentery of the Fallopian tube) and the greater omentum are vascular structures and at autopsy new blood vessels were sometimes noted passing from these structures into the closed peritoneal defect or midline scar.

Discussion

This study shows that intraperitoneal instillation of the newly formulated povidone-iodine/PVP solution (PVP 11 per cent, available iodine 0·1 per cent) at operation results in a highly significant reduction in both the number ($P<0\cdot001$) and the mean length of attachment ($P<0\cdot001$) of adhesions forming in treated rats compared with untreated controls. The fact that povidone-iodine (PVP 1 per cent, available iodine 0·1 per cent) had no effect on the development of adhesions in rats following colectomy (Gilmore, Rosin et al., 1978) suggests that the anti-adhesive effect of the new formulation is due to the increased PVP content.

As might be expected from our previous study (Gilmore and Reid, 1976), noxythiolin 1 per cent significantly reduced the number of adhesions in treated rats compared with rats given Ringer solution ($P<0\cdot05$) and also reduced the mean length of adhesions formed ($P<0\cdot01$). Rats treated with noxythiolin 1 per cent, however, had significantly more adhesions ($P<0\cdot05$) than those treated with povidone-iodine/PVP. The fact that noxythiolin 0·5 per cent was ineffective suggests that the anti-adhesive property of this antiseptic is related to its concentration.

It has been clearly demonstrated that it is not simply the presence of fluid in the peritoneal cavity which prevents adhesions forming. There was no significant difference in the number of adhesions between groups A, B or C, yet only rats in the latter two groups received intraperitoneal fluid.

It is difficult to relate the anatomy of the adhesions formed in this study to man. However, it is interesting to note that the greater omentum was frequently involved with adhesions and that 28·4 per cent of the laparotomy incisions had adhesions. How effective the new povidone-iodine/PVP solution would be in preventing intestinal obstruction due to adhesions in man remains a point of conjecture, since its use did not completely eliminate their formation in rats.

There are three possible reasons for the anti-adhesive effect of noxythiolin. O'Meara showed it to have anticoagulant properties, thus preventing fibrin deposition (Garratt, 1969). Its topical cytotoxic

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ad [illegible] an [illegible] PV [illegible] since [illegible] mo [illegible] Expe [illegible] Goto [illegible] indica [illegible] affect [illegible] division by slow [illegible] contact inhibition, thus cells [illegible] agglutinability. This seems the most likely explanation of the anti-adhesive effect of povidone-iodine/PVP solution. But again, as with noxythioloin, the solution's antiseptic properties probably also played a part.

We have shown in the rat that treatment with a newly formulated povidone-iodine/PVP solution is significantly more effective in reducing the number of peritoneal adhesions forming than is treatment with Ringer solution and noxythiolin 0·5 per cent and 1·0 per cent. A standard povidone-iodine has been shown to reduce significantly the mortality of mice and rats with peritonitis (Gilmore, Reid et al., 1978). It seems unlikely that the newly formulated mixture used in the present study loses its antiseptic properties when the additional PVP is added, since the chemical reaction between PVP and iodine is taken to completion when they are combined initially (Siggia, 1957).

This new solution with its antibacterial and anti-adhesive properties would appear to have considerable potential in all operations involving mesothelial surfaces.

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References

ARMITAGE P. (1973) A comparison of several groups. In: *Statistical Methods in Medical Research.* Oxford, Blackwell Scientific, pp. 189–197.

BADOWSKI A. and DACIEWICZ Z. (1971) The importance of high molecular weight colloid substances in the prevention of experimental peritoneal adhesions. *Polish Med. J.* **10**, 147–153.

BOY[illegible] F. (1942) The prophylaxis of peritoneal adhesions: a review of the literature. *Surgery* **11**, 118–168.

DESAI S. and JAMIESON C. W. (1973) Intraperitoneal noxythiolin as an experimental chemotherapeutic agent. *Br. J. Surg.* **60**, 350–351.

[illegible]S H. (1962) The aetiology of postoperative abdominal adhesions. An experimental study. *Br. J. Surg.* **50**, [illegible]6.

[illegible] (1971) The cause and prevention of postoperative intraperitoneal adhesions. *Surg. Gynecol. Obstet.* **133**, 497–511.

ELLIS H. (1974) Intraperitoneal adhesions. *Br. J. Hosp. Med.* **11**, 401–408.

GARRETT M. J. (1969) Adjunctive antibacterial instillation in radiotherapy of carcinoma of the bladder. *Br. J. Clin. Pract.* **23**, 10.

GILMORE O. J. A. and REID C. (1976) Noxythiolin and peritoneal adhesion formation. *Br. J. Surg.* **63**, 978–980.

GILMORE O. J. A. and REID C. (1978) Prevention of peritoneal adhesions by a new povidone-iodine/PVP solution. *J. Surg. Res.* **25**, 477–481.

GILMORE O. J. A., REID C., HOUANG E. T. et al. (1978) Intraperitoneal povidone-iodine in peritonitis. *J. Surg. Res.* **25**, 471–476.

GILMORE O. J. A., ROSIN R. D., EXARCHAKOS G. et al. (1978) Colonic anastomosis healing: the effect of topical povidone-iodine. *Eur. Surg. Res.* **10**, 94–104.

GOTO M., KATAOKA Y., KIMURA T. et al. (1973) Decrease of saturation density of cells of hamster cell lines after treatment with dextran sulphate. *Exp. Cell Res.* **82**, 367–374.

JACKSON B. B. (1958) Observations on intraperitoneal adhesions. *Surgery* **44**, 507–514.

JAMIESON C. W. (1972) Inhibition of the growth of tumour cells in culture by noxythiolin. *Br. J. Surg.* **59**, 108–109.

KALLIGIANNIS O. (1961) Postoperative Adhasionsprophylaxe durch Kollidone. *Beitr. Klin. Chir.* **27**, 365–367.

KROOK S. S. (1947) Obstruction of the small intestine due to adhesions and bands. An investigation of the early and late results after operative treatment on aetiological study of recurrence. *Acta. Chir. Scand.* **95**, Suppl. 125.

MAZUJI M. K., KALAMBAHETI K. and PAWAR B. (1964) Prevention of adhesions with PVP. *Arch. Surg.* **89**, 1011–1015.

MULLER G. P. and RADEMAKER L. A. (1933) Role of infection in the production of postoperative adhesions. *Arch. Surg.* **26**, 280–287.

OETELL V. H. ROTHLANDER H. and SCHULZE W. (1954) Bericht über ein neus verfahren zur verhütung von banchfellvernachsungen durch Kollidon. *Chirurgie (Abdomen)* **72**, 177–178.

SIGGIA S. (1957) The chemistry of povidone iodine. *J. Am. Pharm. Assoc.* (Scientific Edition) **46**, 201–204.

UPPLEGGER H. (1956) Prevention of peritoneal adhesions by Kollidon. *Chirurgie* **27**, 365–367.

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Mercury nephrotoxicity from peritoneal lavage

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AND SQUADRON LEADER D. J. RAINFORD*

SUMMARY
Two cases of acute renal failure following intraperitoneal administration of mercury are described.

MERCURIC chloride is a known nephrotoxin, causing renal failure in acute poisoning and nephrotic syndrome following prolonged exposure. In this report we present 2 cases of acute renal failure following intraperitoneal administration of mercury. One patient subsequently developed nephrotic syndrome.

Case reports

Case 1: A 61-year-old woman presented in July 1976 with a history of abdominal discomfort and swelling. At laparotomy she was found to have a large ovarian cyst which ruptured on removal. Because of the possibility of malignancy, peritoneal lavage was performed with a 1 : 2000 solution of mercuric chloride. Postoperatively she became severely hypotensive with abdominal distension. Bleeding was suspected, but repeat laparotomy revealed an intense exudative peritoneal reaction. Urine output fell to 350 ml in the following 24 h despite fluid replacement and high doses of frusemide. The patient was transferred to the renal unit where the diagnosis of established oliguric acute renal failure was confirmed. Mercury levels on admission were raised in serum (12 mmol/l) and urine (1400 nmol/l) (normal urinary level up to 100 nmol/l). The patient's initial blood urea was 24 mmol/l, rising to 36 mmol/l by the fourth postoperative day, when haemodialysis was commenced. She required daily dialysis for 9 days before a diuresis ensued, with a spontaneous fall in blood urea by the eighteenth postoperative day.

The patient's urine was protein-free on discharge, but on routine follow-up in January 1977 she was found to have the nephrotic syndrome. Despite symptomatic treatment with diuretics and salt-poor albumin infusions, urinary levels rose to 53 g/24 h and she became increasingly oedematous. Renal biopsy showed minimal change of the glomeruli and mild interstitial nephritis. She was treated with high dose intravenous methyl prednisolone pulses with a rapid fall in urinary protein. Remission was maintained on oral prednisolone for 6 months and there has been no recurrence of proteinuria since stopping therapy.

Case 2: A 50-year-old woman presented in August 1976 with a history of abdominal pain and altered bowel habit. Barium enema was suggestive of malignancy and laparotomy in October 1976 confirmed a localized carcinoma of the descending colon, for which a left hemicolectomy was performed. Peritoneal lavage with a 1 : 500 solution of mercuric chloride was carried out. Postoperatively she became severely hypotensive with signs of peritonitis. Resuscitative measures restored cardiovascular stability, but urine output remained fixed at between 1 and 1·5 l/24 h and was of low and inappropriate osmolality. Blood urea rose to 46 mmol/l by the tenth postoperative day and established non-oliguric acute renal failure was diagnosed. The serum mercury level when the patient was first seen was 11·9 mmol/l. A mobile dialysis team from the renal unit commenced haemodialysis. Daily dialysis was required for 6 days before a diuresis ensued, with a spontaneous fall in blood urea by the nineteenth postoperative day. There has been no significant proteinuria on follow-up to date.

Discussion

These two cases illustrate the potential hazard of peritoneal lavage with mercuric chloride. This technique has been used for many years in the belief that mercury exerts a cyt[illegible] on any malignant cells remaining post[illegible] [illegible]ent work suggests, however, that this form [illegible]ent is no more effective than lavage with sterile [illegible]

The clinical aspects of mercury nephrotoxicity have been well reviewed (Schreiner and Maher, 1965; Hollenberg et al., 1970), as has the mode of action of mercury in causing acute renal failure (Oken, 1972). We have found one previous report of acute renal failure following peritoneal lavage with a 1 : 500 solution of mercuric chloride (Gingell et al., 1967).

In our cases, the acute renal failure may have been the result of absorption of toxic quantities of mercury, combined with the hypotension which resulted from the exudative peritoneal reaction in each case. An inflamed peritoneum would enhance absorption of mercury, and the hypotension would increase its nephrotoxic potential. There was no other obvious cause for the acute renal failure and the hypotension alone was not thought to be severe enough to explain it.

The onset of nephrotic syndrome in one of our cases is further supportive evidence that mercury toxicity was involved in the initial illness. No other cause for nephrotic syndrome was found. The renal biopsy changes of mercury-induced nephrotic syndrome are legion and the presence of only minor changes is quite consistent with the diagnosis.

Many patients treated with intraperitoneal mercuric chloride do not develop acute renal failure, although the recommended concentration for use on raw surfaces is lower than that used in our cases. Perhaps an intense chemical peritonitis represents an idiosyncratic reaction to the drug? However, in the absence of firm evidence that the treatment is effective, one can only echo Schreiner's words from 13 years ago: 'The use of mercuric salts for douching and surgical irrigation should be discouraged' (Schreiner and Maher, 1965).

Acknowledgement

We would like to thank the Director General of Medical Services (RAF) for permission to publish this paper.

References

GINGELL J. C., CLEGG J. and WALLACE M. (1967) Mercury perchloride in surgery. *Br. Med. J.* 3, 867.

HOLLENBERG N. K., ADAMS D. F., OKEN D. E. et al. (1970) Acute renal failure due to nephrotoxins. *N. Engl. J. Med.* **282**, 1329–1334.

OKEN D. E. (1972) Modern concepts of the role of nephrotoxic agents in the pathogenesis of renal failure. *Prog. Biochem. Pharmacol.* 7, 219–247.

SCHREINER G. E. and MAHER J. F. (1965) Toxic nephropathy. *Am. J. Med.* **38**, 409–449.

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gation: a survey of patient opinion

RRICOTT, M. R. B. KEIGHLEY, G. D. OATES
LIAMS*

SUM. [illegible]
Patients [illegible] rrigation via a naso-gastric t[illegible] by a questionnaire answered b[illegible] nts who received this method of bowel pre[illegible] before operation on the large bowel or colonoscopy. Abdominal pain during the irrigation was experienced by 13 patients (17 per cent) and nausea and vomiting occurred in 24 (30 per cent). Intubation with a nasogastric tube and the discomfort of prolonged sitting on a commode were considered the most disagreeable aspects of the procedure. Fifty-six patients (71 per cent) would have agreed to the irrigation being repeated if necessary and many patients preferred whole gut irrigation to previous 'orthodox' bowel preparations that they had experienced.

WHOLE gut irrigation as a method of washing the bowel clean has come into use in many centres since it was first described by Hewitt et al. in 1973, and the technique is now often used for bowel preparation before operation, colonoscopy and radiology. Three years ago we reported our experience in 81 patients (Crapp et al., 1975) and we have continued to use this method of preparation before colonoscopy and operation.

Although the procedure is widely used in several hospitals, some nurses and doctors consider it too distressing for the patient and others believe the technique to be dangerous. Attempts have been made to assess patient acceptance of whole gut irrigation. Levy et al. (1976) studied 21 patients prepared for barium enema examination and also for colonoscopy. For one investigation they were prepared by oral castor oil and cleansing enemas and for the other by drinking isotonic saline at the rate of 1 l/40 min. Sixteen (76 per cent) patients preferred the lavage. Hewitt et al. (1973) reported that 2 of the 6 patients who had experienced both whole gut irrigation and conventional large bowel preparation with cathartics and enemas preferred irrigation. The purpose of this paper is to report the results of a survey of our patients' acceptance of the procedure and to recommend modifications to increase acceptability.

Patients and methods

Method of irrigation

Patients were admitted to hospital on the day before operation or colonoscopy. No dietary restrictions were imposed and the procedure was explained to the patient. The subject was weighed before and after irrigation. A 'Salem' sump tube (size 14) was passed via the nose and the patient seated on a commode. Intramuscular metoclopramide (10 mg) was given before irrigation and as necessary throughout the procedure to control nausea and abdominal distension. Isotonic saline at 37 °C, without potassium supplements, was used as an irrigant. The saline was delivered by conventional gravity feed in the majority of irrigations, but this was later substituted by a Watson–Marlow Flow Inducer (MHRE 22), which gave a constant rate of infusion and was less cumbersome for the nursing staff to use. The maximum flow rate for each subject was regulated to as fast as possible without producing symptoms of nausea and abdominal distension, and varied between 2 and 4 l/h. Urine output was recorded and the procedure stopped when the anal effluent became clear. The mean time taken was 3½ h (range 2–6).

Questionnaire (Table I)

Ninety-nine patients who had received whole gut irrigation between July 1976 and December 1977 were sent questionnaires. All were questioned within 1 month of hospital discharge. Fifty-two of the patients had been prepared for colonoscopy and 47 had been prepared for an operation on the large bowel. Seventy-nine (80 per cent) questionnaires were completed and returned. The average age of the 79 patients was 53·8 years (range 17–84 years). Forty-three were male and 36 female.

Table I: REPLIES TO THE QUESTIONNAIRE ON WHOLE GUT IRRIGATION (79 PATIENTS)

	Yes	No	No answer
Part I			
1. Did you understand why this cleaning of the bowel was being performed?	77	1	1
2. Were you apprehensive or afraid?	30	47	2
3. During the procedure did you experience:			
a. Pain?	13	64	2
b. Feeling of sickness?	29	49	1
c. Vomiting?	24	54	1
d. Discomfort in the back passage?	12	66	1
e. Discomfort from sitting on the commode?	49	27	3
4. After it was finished did you feel unwell?	25	54	0
Part II			
5. Which of the following did you consider the most disagreeable:			
a. Passing of the tube into the stomach?	46		
b. Discomfort of sitting?	23		
c. Stomach pains?	1		
d. Embarrassment of the procedure?	5		
e. None?	4		
6. If it was necessary to perform the cleaning again would you—			
a. Agree without hesitation?	30		
b. Agree but worry about it?	26		
c. Consider refusing but feel it was necessary?	19		
d. Refuse?	4		

Results

The results of the questionnaire are shown in *Table I*. Although 77 of the 79 patients (97 per cent) understood why the irrigation was being performed, 30 (38 per cent) admitted to being afraid of the procedure. Forty-six (58 per cent) found the presence of a nasogastric tube the most distressing part of the method, but 23 (29 per cent) considered that the discomfort of sitting on the commode was more disagreeable. Discomfort from prolonged sitting was experienced by 49 patients (62 per cent). Nausea was

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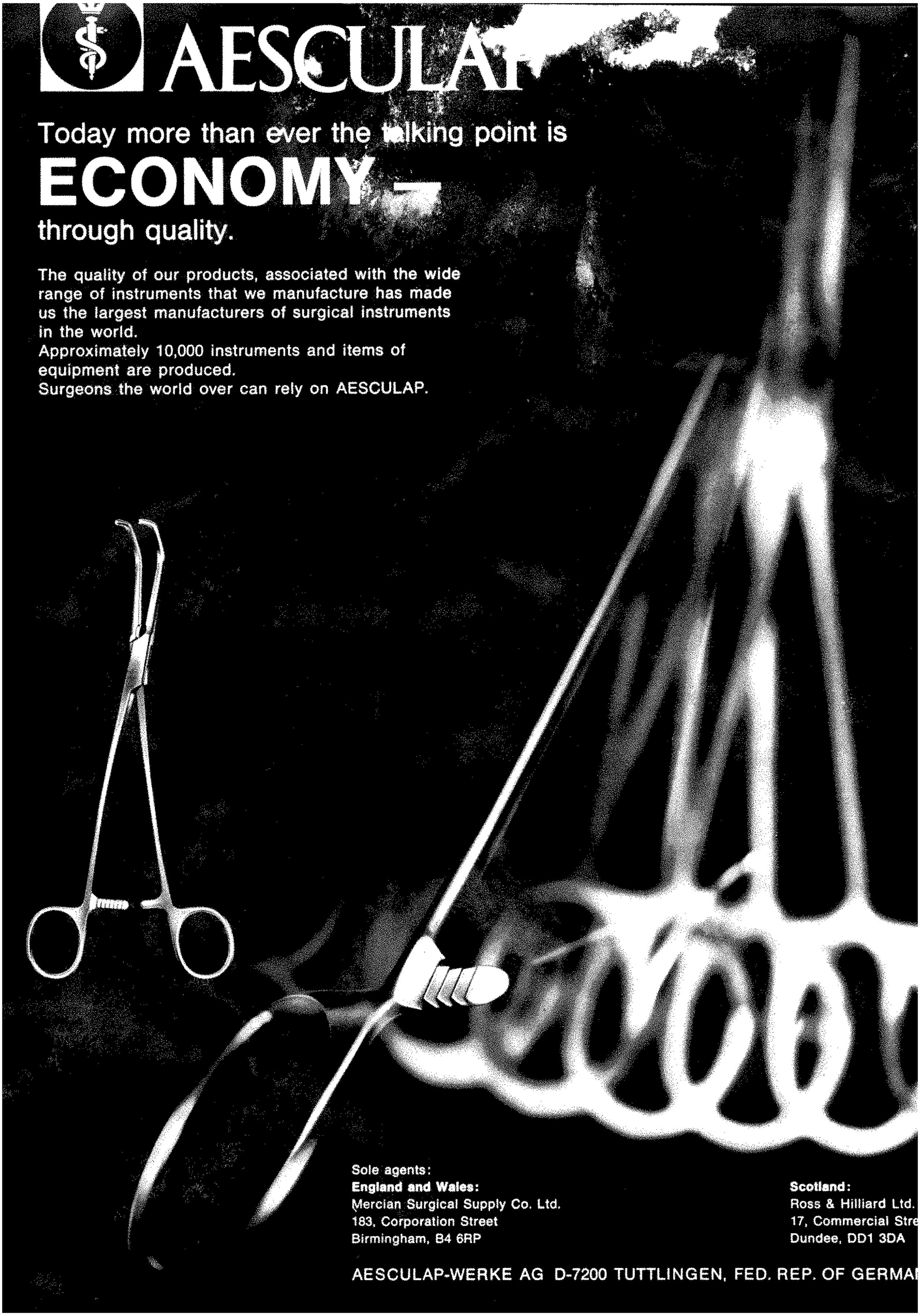

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Br. J. Surg. Vol. 66 (1979) 203–206

A new appliance for collecting ileostomy and jejunostomy fluid in the postoperative period

G. L. HILL AND I. R. PICKFORD*

SUMMARY

A new lightweight two-piece ileostomy appliance was tested in 11 patients with newly established ileostomies and jejunostomies. Seven of the patients presented difficult stoma care problems. The appliance was fitted in theatre on completion of the operation and the patient was followed until discharge from hospital.

The appliance remained in place for an average of 4·8 ± 1·2 days. In a total of 204 patient-days the pouch became dislodged from the flange on 10 occasions and there was leakage under the body flange on 7 occasions. All but one of the patients continued to use the appliance on discharge. No patient was allergic to the appliance nor complained of odour.

It is concluded that this new appliance represents an important advance in postoperative stoma care.

WITH the widespread use of the eversion type of ileostomy and immediate mucocutaneous suture it has become the custom to apply an adherent ileostomy appliance in theatre, as soon as the ileostomy has been established. The ideal appliance for this purpose needs to be leakproof and odourproof, lightweight and able to be easily adapted for final use. It should also be in two pieces, so that the bag can be removed to allow easy access to the stoma without having to separate and reapply the adherent flange.

In this paper we describe our experience with a new ileostomy appliance which fulfils many of these criteria. We have used it in a group of particularly difficult patients with newly established ileostomies and jejunostomies.

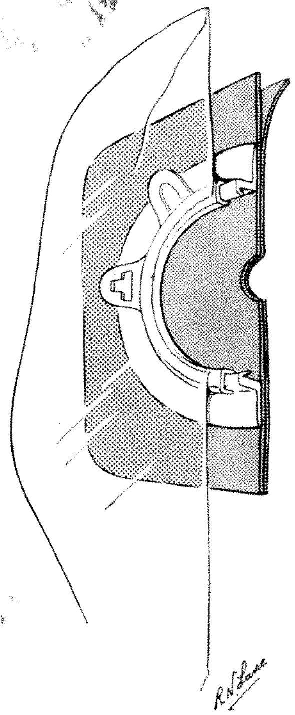

Fig. 1. The appliance consists of a transparent plastic pouch connected to a body flange via a snap lock.

Patients and methods

The appliance

The two-piece appliance (Surgicare System 2, Squibb & Sons Ltd) is based on the skin barrier Stomahesive, a preparation of pectin and methylcellulose (gelatin 20 per cent, pectin 20 per cent, sodium carboxymethylcellulose 20 per cent, polyisobutylene 40 per cent). It consists of a body flange and drainable bag (*Fig.* 1). The body flange is a 4-in (approx. 100-mm) square of Stomahesive attached by means of a double-sided adhesive disc to a low density polethylene injection-moulded flange. The transparent drainable bag is made of a trilaminate plastic sheeting 75 μm thick. Welded to the bag, around the point of stoma entry, is an ethylene vinyl acetate flange, which is the corresponding component to the flange attached to the Stomahesive square. The two flanges seal together via an ingenious type of snap lock (*Fig.* 2). The end of the drainable bag is sealed with a polypropylene clip.

Fitting of the appliance

The flange unit is applied to the new stoma as soon as the mucocutaneous sutures have been inserted and the surrounding skin has been prepared. The skin is cleansed with cetrimide and carefully dried before being thoroughly de-greased with ether. Attention is then turned to preparing the flange unit for application. When selecting the correct flange size it must be remembered that swelling of the stoma can occur and it is important that the diameter of the opening in the face plate allows at least 0·5 cm for expansion. In most patients a flange with an internal diameter of 45 mm (1¾ in) can be used but other diameters (28 mm, 57 mm and 70 mm) are available.

The centre hole in the Stomahesive flange unit is not enlarged directly. If radial slits are made (*Fig.* 3) and the opening is gently shaped with the fingers so that it will fit snugly over the stoma (*Fig.* 4) a very adequate watertight seal can be obtained. The silicone release paper covering the skin side of the Stomahesive is then removed and the whole flange unit is positioned over the stoma and pressed firmly on to the skin (*Fig.* 5). If the surgeon has removed his gloves before this manoeuvre the warmth from his hands aids adherence of the Stomahasive to the skin. It is advisable to take a little time holding the flange in this way, because it will then mould to the contours of the skin and prevent channelling of small bowel fluid. Care is taken to ensure that the seal around the circumference of the stoma is also complete. The pouch is then attached to the flange unit via the snap lock, remembering to position the outlet in the flank so that drainage will be facilitated while the patient is lying in bed (*Fig.* 6).

Patients

We have used the new appliance on 11 patients in whom we have recently performed an end ileostomy or jejunostomy. Although 4 of these patients had well-made, normally functioning ileostomies the others had stomas that were far from ideal (*Table I*). Among these were 3 patients with jejunostomies and

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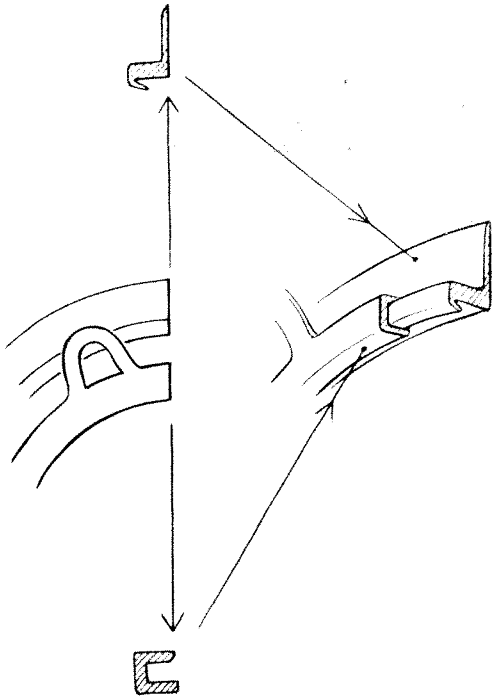

Fig. 2. The snap lock.

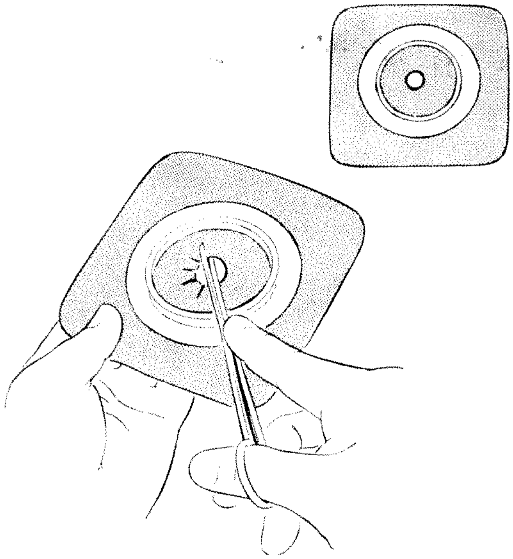

Fig. 3. Preparing the body flange: radial slits are made in the Stomahesive.

each of these had flush stomas with daily faecal outputs of 1–3 l. There was also a male patient (*Case* 5) who had a particularly difficult stoma which was large, swollen and oedematous and passed profuse amounts of loose ileostomy fluid.

Results

Acceptability

In all but one of the patients, *Case* 5, the appliance proved to be comfortable and no patient was sensitive

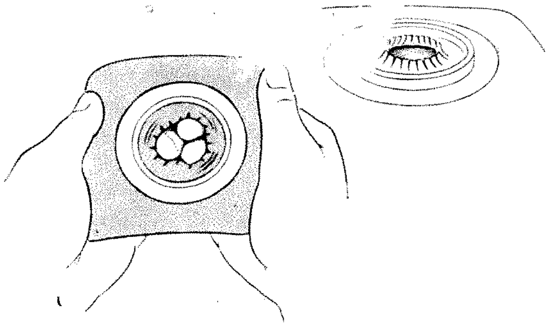

Fig. 4. Preparing the body flange: the opening is shaped to accommodate the stoma.

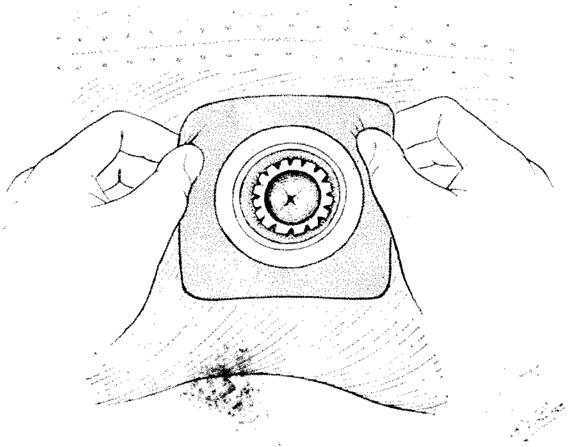

Fig. 5. The body flange is sited over the stoma and the Stomahesive is held on to the skin aiding adhesion with the warmth of the hands.

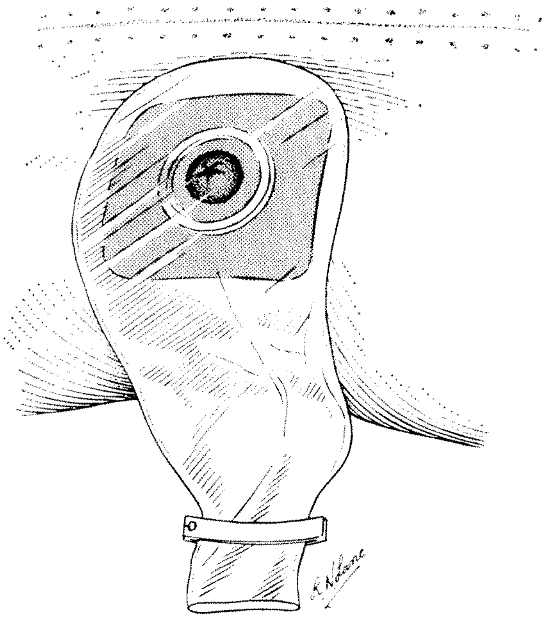

Fig. 6. The pouch is snapped on to the body flange: the opening of the pouch lies in the flank.

Table I: DETA[illegible] OF [illegible]ATIENT SERIES

Case	Age (yr)	Sex	Type of stoma	Stoma problem	Size of appliance used (mm)	Days in hospital after surgery	Total no. of appliances used	Complications		Final outcome
								D	L	
1	51	F	Ileostomy: output 0·5 l/d	Obese patient, flush stoma	45	28	5	1	0	Home with appliance
2	60	F	Ileostomy: output 0·5 l/d	Obese patient, normal stoma	45	8	2	1	0	Home with appliance
3	40	F	Jejunostomy: output 2–3 l/d	Flush stoma	45	12	3	1	2	Home with appliance
4	48	F	Ileostomy: output 1–2 l/d	Normal stoma	45	7	2	1	0	Home with appliance
5	56	M	Ileostomy: output 1–1·5 l/d	Large swollen stoma	75	8	3	3	0	Changed to another two-piece appliance
6	52	F	Ileostomy: output ≃ l/d	Moderately obese, very short stoma	45	28	6	1	0	Home with appliance
7	40	F	Jejunostomy: output 2–3 l/d	Flush stoma	45	28	6	0	3	Home with appliance
8	47	F	Ileostomy: output 0·5–1 l/d	Flush stoma	45	35	6	2	1	Home with appliance
9	31	M	Ileostomy: output ≃ 1 l/d	Normal stoma	45	31	5	0	1	Home with appliance
10	71	M	Ileostomy: output 1–2 l/d	Normal stoma	45	7	1	0	0	Home with appliance
11	39	F	Jejunostomy: output 1–1·5 l/d	Flush stoma	45	12	3	0	0	Patient still in hospital using the appliance

D, displacement; L, leakage.

to the Stomahesive body flange. With practice the nurses were able to secure the snap lock with sufficient gentleness to avoid undue pain. During the recuperative phase all the patients quickly learned how to manage the appliance and the ease of the snap lock system proved to be a real help when excessive gas had to be released. Offensive odour was never complained of and the medical and nursing staff generally felt that the appliance was odour-free.

Ten of the patients are now home and all but one are continuing to use the appliance (*Table I*). Each claims to be satisfied with it. *Case* 5, who had a large and swollen stoma, was never happy with the appliance, which had become dislodged on three occasions during his hospital stay, and he now uses a two-piece appliance consisting of a large rubber flange and a black rubber drainable bag.

Complications

Over the entire study period the body flange remained in place for an average of 4·8 ± 1·2 days (range 2–7 days). In 7 patients the bag became disconnected from the body flange on at least one occasion (10 times in 204 patient-days). In each case the bag had become overfull and a sudden movement by the patient had pulled the snap lock apart. In 4 patients leakage occurred when the body flange lifted from the skin. Three of these patients had stomas that were flush with the skin and leakage had occurred under the body flange in the region of the mucocutaneous junction. *Case* 7, 4 weeks after the establishment of a flush jejunostomy, now finds it necessary to change the whole appliance every 1 or 2 days because of skin irritation consequent upon leakage under the Stomahesive barrier. No other patient has severe peristomal skin soreness. On three occasions, when a patient had been moving about with the pouch full of fluid, the Stomahesive split near the circumference of the polyethylene flange. This quickly resulted in leakage and a new body flange was required.

Discussion

Although the patient is usually very ill and passive after ileostomy surgery important long term attitudes are developed during the postoperative period. Experiences with the stoma at this early stage have an important influence upon the patient's subsequent recovery and rehabilitation. Clearly it is of crucial importance that the patient sees that the stoma works well. Leakage, skin irritation and nauseating odour raise fears and increase doubts in the patient's mind as to his ability to cope with this new situation. Thus, any new appliance which functions well in the postoperative period and is free from troubles such as leakage, skin irritation and odour is an important advance in this difficult branch of surgery. Although it is not perfect, the results show that this new appliance, used here on a particularly difficult group of patients, has worked well. All the patients have found it to be light and simple to use.

Before the appliance can be confidently recommended for long term use, however, a more formal trial, in a wide variety of patients, is required. On the other hand, we have little hesitation in recommending its use in the recovery phase after stoma surgery.

The Stomahesive body flange, as might be expected, proved very satisfactory. On only 7 occasions in more than 200 days did leakage occur under the flange. Since the first full length trial of Stomahesive (Kyte and Hughes, 1970), there has been a growing awareness that it is one of the best available barriers against corrosive small bowel contents. A recent study (Marks, 1978) showed that Stomahesive produced the lowest degree of skin irritation when compared with several other widely used adhesives. Until recently it has been used in enterostomal therapy as an adhesive skin barrier under a variety of face plates and adhesive pouches. Although such arrangements have proved very helpful in some patients, they are rather cumbersome and somewhat complicated to use. Clearly, this new two-piece appliance, in which a light plastic pouch is simply snapped on to a square of [illegible] is an important advance.

One of the crucial parts of the [illegible] lock which connects the pouch to the [illegible] spite of our initial doubts, the snap lock [illegible] generally functioned well. Our study has shown, however, that it is not perfect, for when the pouch becomes overfull and heavy, vigorous movement can dislodge it. This problem is infrequent (10 times in 204 days) and can be avoided in most instances, although it is extremely distressing for the patient when it occurs. On the other hand, the snap lock has major advantages. The knack of fastening the lock is quickly acquired and it is most helpful to be able to remove the pouch to examine the stoma or release excessive gas.

Of major importance to the convalescent patient is the gas transmission qualities of the pouch material. New generation plastics and plastic laminates are becoming increasingly popular as pouch materials [illegible] from this [illegible].

In conclusion, we feel that this is the best [illegible] appliance we have used for the postoperative care of small bowel stomas. It is not yet the last word, but it works well and is worth the attention of all surgeons who perform this type of surgery.

References

KYTE E. M. and HUGHES E. S. R. (1970) Peristomal skin protection with 'Orahesive'. *Med. J. Aust.* **2**, 186–187.

MARKS R. (1978) Choice of adhesives in stoma care. Paper read at the International Ostomy Association Meeting, Milan, March 1978.

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acute urinary

SALEM AND IAN RAMSAY*

SUMMARY

Three elderly patients presented at one hospital in a 2-week period with acute urinary retention precipitated by the hyperosmolar non-ketotic diabetic state. In each case routine urine testing was reported as showing 1 per cent glycosuria. The first two patients were admitted at night and blood glucose estimations were not done. This led to a delay of 16 and 12 h respectively before the appropriate therapy was instituted. It is suggested that this clinical presentation, previously unreported, may not be a rarity and represents an avoidable cause of death in patients with acute urinary retention.

THE hyperosmolar non-ketotic diabetic state (HNKDS), with or without coma, usually occurs in elderly diabetics, often with previously unrecognized disease. Subclinical prostatism is common in this age group. Surprisingly, acute urinary retention as the presenting feature of the diabetic hyperosmolar state has not been reported in the literature before. We would like to report 3 patients, subsequently diagnosed as having HNKDS, who were all admitted to one hospital within a period of 2 weeks because of acute urinary retention.

Case reports

Case 1: A 69-year-old man, not previously known to be diabetic, was admitted to the surgery department at 1.00 a.m. with acute urinary retention. He had last passed urine 26 h before admission. He gave a history of thirst and polyuria for 3 weeks and of stress incontinence for 1 week. There was no other previous history of urinary symptoms. He had taken no drugs apart from dextropropoxyphene (Distalgesic) for his cervical spondylosis.

On examination he was found to be dehydrated. His drowsiness was attributed to his urological condition. His bladder was palpable up to the umbilicus and rectal examination revealed an enlarged, smooth prostate. No obvious neurological abnormality was found. Catheterization yielded 2000 ml of urine which was said to contain 1 per cent glucose and 1+ of albumin. The initial urea and electrolyte estimations are shown in *Table I.* He was treated with dextrose saline infusion, 500 ml every 4 h with 1 g of potassium in alternate bottles. Fluid balance charts showed that a polyuria of 4000 ml/6 h was occurring. Urine testing with Multistix (Ames Ltd) continued to be reported as showing 1 per cent glycosuria. However, his condition was deteriorating; 16 h after admission his blood glucose was 45 mmol/l and he was referred to the physicians. The further investigations are shown in *Table I.* He was given 30 units of soluble insulin intravenously and 30 units intramuscularly and received 4 l of half-strength normal saline with supplementary potassium. Four hours later he was given a further 80 units of insulin intravenously. Despite a falling blood glucose his condition continued to deteriorate and he died 24 h after admission.

Case 2: An 83-year-old man, not known to be diabetic, was admitted to the surgery department at 1.00 a.m. with acute urinary retention. He was drowsy, confused and dehydrated. Subsequently he was able to give a history of thirst and weight loss for 6 months, polyuria for several weeks and retention of urine for approximately 12 h. He had not received any drugs. There was no history of hesitancy or terminal dribbling. The bladder was palpable up to just below the umbilicus. The prostate did not feel enlarged on rectal examination and only soft faeces were present. Neurological examination revealed no abnormality. Catheterization obtained 1200 ml of urine and Multistix examination was reported as showing 1 per cent glucose. The initial urea and electrolytes are shown in *Table I.*

Twelve hours later the patient was more confused and unwell. He had pulled his catheter out and the bladder was once again palpable. A blood glucose estimation was done and found to be 52 mmol/l; the patient was then referred to the physicians. He was treated with half-strength normal saline, insulin and heparin. Within 9 h his blood glucose had fallen to 8·3 mmol/l and 2 days later he had fully recovered and was up and about. A CSU was sterile and no abnormality was found on microscopy. Subsequently he had no significant urinary obstructive symptoms but an intravenous pyelogram did show a trabeculated bladder and a small residual volume after micturition. His diabetes was well controlled on diet and glibenclamide 5 mg per day.

Case 3: A 76-year-old male Cypriot diabetic, treated by diet alone, was referred to the surgical department with acute urinary retention at 11.00 a.m. He was distressed and dehydrated, could not speak English, but pointed to his lower abdomen. His bladder was palpable up to his umbilicus and his prostate was slightly enlarged. Neurological examination was normal apart from absent ankle jerks. Catheterization yielded 1500 ml of urine. Testing with Multistix was reported as showing 1 per cent glucose. Because of the experience with the previous two patients he was referred to the physicians. Blood glucose and electrolyte estimations confirmed the diagnosis of a hyperosmolar diabetic state. The initial investigations are summarized in *Table I.*

He was treated with half-strength normal saline, heparin and both intravenous and intramuscular soluble insulin. At 24 h after admission his blood glucose was 7·8 mmol/l and he was feeling generally quite well apart from some breathlessness. A CSU showed no microscopic abnormality and was sterile on culture.

Through an interpreter he gave a history of chronic bronchitis for many years. He had been unwell for 1 week before admission, with thirst and polyuria, but until he developed urinary retention had not had any obstructive symptoms. He had not been on any drugs. His ECG showed ventricular ectopic beats and some ischaemic changes. Four days after admission he went into acute left ventricular failure which did not respond to treatment and he died.

Discussion

The hyperosmolar diabetic state is associated with massive diuresis secondary to severe hyperglycaemia; this results in marked dehydration, haemoconcentration and hyperosmolality. At the time of presentation most patients are either in pre-coma or coma (Halmos et al., 1966). Although subclinical benign prostatic hypertrophy occurs in 73 per cent of men above the age of 60 (Franks, 1954), it is surprising that acute urinary retention has never been reported as the initial presentation of the hyperosmolar non-kinetic diabetic state (HNKDS).

Acute urinary retention is usually considered a surgical emergency and patients with HNKDS presenting in this way would thus be admitted under the surgeons. This happened in all three of our patients

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Table I: RESULTS OF PRELIMINARY INVESTIGATIONS IN ALL 3 PATIENTS

	Blood urea (mmol/l)	Pl. Na (mmol/l)	Pl. K (mmol/l)	Pl. Cl (mmol/l)	St. bicarb. (mmol/l)	Total proteins (g/l)	Blood glucose (mmol/l)	pH	Pl. osm.* (mosmol/l)	Urine (%) glucose	Urine ketones	Urine albumin
Normal value	2·5–6·4	135–148	3·5–5·3	98–108	21–28	60–82	3·9–5·8	7·35–7·45	285±5			
Case 1	27·1	162	2·9	125	22	72	45	7·27	402	1	0	+
Case 2	25·8	150	5·6	105	24	72	52	7·37	389	1	0	0
Case 3	32·0	152	3·8	100	24	81	78	7·34	422	1	0	++

Pl, plasma; St. bicarb., standard bicarbonate.
* Calculated according to the method of Jackson and Forman (1966).

and resulted in a delay of 16 and 12 h respectively in the first two patients before the start of appropriate treatment. As in all acute diabetic metabolic disturbances, the earlier the treatment the better the prognosis (Arieff and Carroll, 1972) and this is especially true for the hyperosmolar diabetic state, which usually occurs in elderly patients and is associated with a high mortality rate (Danowski and Nabarro, 1965; Field, 1976). The first patient died in the acute phase of hyperosmolality; permission for post-mortem examination could not be obtained. The third patient died from intractable left ventricular failure 4 days after admission following full correction of the hyperosmolar state. The second patient is alive and well 14 months after his original admission. None of the factors known to precipitate HNKDS, such as diuretic therapy (Field, 1976), was present in our patients.

In any patient with acute urinary retention an underlying precipitating factor should always be sought. None of our patients had obvious evidence of diabetic neuropathy. Urine testing with Multistix was clearly a factor contributing to the delay of treatment in the first two patients. In each case the result was recorded as 1 per cent, and this was not thought by the surgeons to warrant an emergency blood-glucose estimation during the night. In fact it can be difficult to differentiate between a glycosuria of 1 per cent and 2 per cent or more using Multistix. A more easily quantifiable method of estimating glycosuria such as Clinitest (Ames Ltd) would have probably alerted the admitting doctor to the serious nature of the patients' condition and would have led to more prompt investigation and treatment.

We suggest that any degree of glycosuria in an elderly patient with acute urinary retention should be immediately checked by a blood-glucose estimation. Urea, electrolytes and osmolality should also be measured as, occasionally, considerable hyperosmolality can occur in the face of moderate hyperglycaemia (Jarrett and Bacon, 1963; Danowski and Nabarro, 1965). The fact that we saw three patients with HNKDS presenting at one hospital with acute urinary retention during a 2-week period may indicate that the condition has been previously overlooked.

References

ARIEFF A. I. and CARROLL H. J. (1972) Nonketotic hyperosmolar coma with hyperglycaemia: clinical features, pathophysiology, renal function, acid-base balance, plasma–cerebrospinal fluid equilibria and the effects of therapy in 37 cases. *Medicine* (*Baltimore*) **51**, 73–94.

DANOWSKI T. S. and NABARRO J. D. N. (1965) Hyperosmolar and other types of nonketoacidotic coma in diabetes. *Diabetes* **14**, 162–165.

FIELD J. B. (1976) Hyperosmolar coma. FAJANS S. S. (ed.) *Diabetes Mellitus*. Bethesda, Maryland, National Institute of Health, pp. 133–141.

FRANKS L. M. (1954) Benign nodular hyperplasia of the prostate: a review. *Ann. R. Coll. Surg. Engl.* **14**, 92–106.

HALMOS P. B., NELSON J. K. and LOWRY R. C. (1966) Hyperosmolar nonketoacidotic coma in diabetes. *Lancet* **1**, 675–679.

JACKSON W. P. U. and FORMAN R. (1966) Hyperosmolar nonketotic diabetic coma. *Diabetes* **15**, 714–722.

JARRETT E. and BACON G. (1963) Hyperosmolarity and diabetic coma. *Lancet* **1**, 891.

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Cytological study of fluid from breast cysts

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SUMMARY

A series of 215 patients with breast cysts has provided 348 specimens of cyst fluid for cytological diagnosis. Only one of these specimens was reported positive for malignant cells and this patient had a carcinoma. Nine specimens were reported as suspicious, but none of these patients had or subsequently developed carcinoma. In 338 specimens cytology was negative. A total of 178 patients (294 specimens) was available for follow-up. Of these 2 proved to have carcinomas on immediate follow-up, i.e. a lump persisted after aspiration, and a further 2 patients developed cancers in the same breast, one 4 and the other 7 years after aspiration. We therefore conclude that the routine submission of breast cyst fluid for cytology is wasteful of time and resources.

We do not propose to discuss the merit of needle aspiration in the management of breast cysts. Controversy has existed in the past as to whether excision biopsy is a safer procedure (Atkins, 1952; Keynes, 1966). We believe, however, that aspiration is now a generally acceptable procedure, and are supported in this view by Patey and Nurick (1953), Schnug and Cavanagh (1966), Forrest (1974), Rimsten et al. (1975) and Rosemond et al. (1977).

We propose to confine ourselves to investigating the value of the routine cytological examination of fluid removed from breast cysts, since it appears that there is a difference of opinion as to its value. Patey and Nurick (1953) appear to have been the first to suggest the importance of cytology in reducing the risk of missing a breast carcinoma (although these authors also stated, somewhat paradoxically, that there was no clear relationship between fibrocystic disease and breast cancer). Their view is supported by Forrest (1974) and Rimsten et al. (1975). Equally, Schnug and Cavanagh (1966) and Rosemond et al. (1977) are of the opinion that cytological examination of cyst fluid is unnecessary.

It appears that the type of carcinoma which may be present can have a bearing on the usefulness of cytological examination and there are two situations to consider. First, in the case of true intracyst carcinoma (*Fig.* 1*a*), cyst fluid cytology could conceivably be valuable; however, the incidence of this particular type of growth is extremely low. Gatchell et al. (1958) quote an incidence of only 0·5 per cent, Kalisher (1977) states that it is 'a rare entity' and Rosemond et al. (1977) quote an incidence of 0·1 per cent. This conclusion has been borne out by our experience in this teaching hospital pathology department, where carcinomas are rarely seen in association with cysts and where intracystic carcinoma is virtually non-existent. If, therefore, we aim to avoid missing these extremely rare tumours by using cytological examination, we shall be assessing a large number of samples totally unnecessarily. If we consider the second situation, the coincidental occurrence of a carcinoma side by side with cysts in the same breast (again, in our experience, an uncommon, though perhaps not rare, situation) (*Fig.* 1*b*), routine examination of cyst fluid is not likely to help in this case as the growth is at some distance from the cyst and cannot be expected to exfoliate cells into the cyst fluid. It should be noted, however, that decompression of the cyst may well make the carcinoma easier to feel clinically.

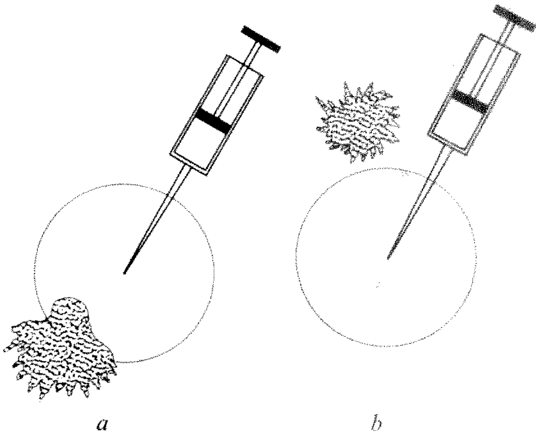

Fig. 1. (*a*) A true cystic carcinoma; (*b*) carcinoma coincidental with a breast cyst.

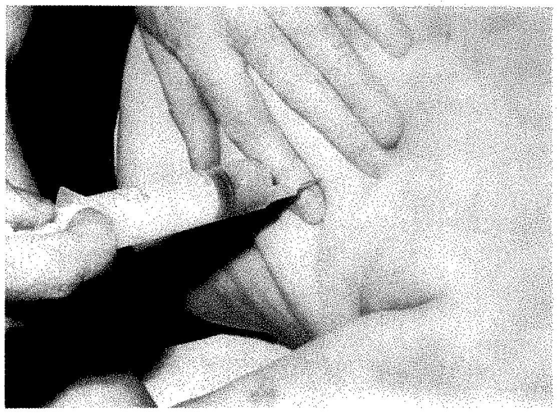

Fig. 2. Needle aspiration of a breast cyst.

Having analysed the problem in this way it appeared to us, on theoretical grounds at least, that it was highly improbable that routine cytology of aspirates from breast cysts was likely to be of any significant value whatsoever as regards detecting an occult carcinoma, and we felt impelled to re-examine the logic of this exercise. We were influenced in this by a retrospective study by one of us (P. N. C.), who had reviewed 106 specimens from 83 patients with breast cysts collected between 1964 and 1970. No malignant cells were found in any of these specimens and of the 67 patients who could be followed up, none subsequently developed breast cancer.

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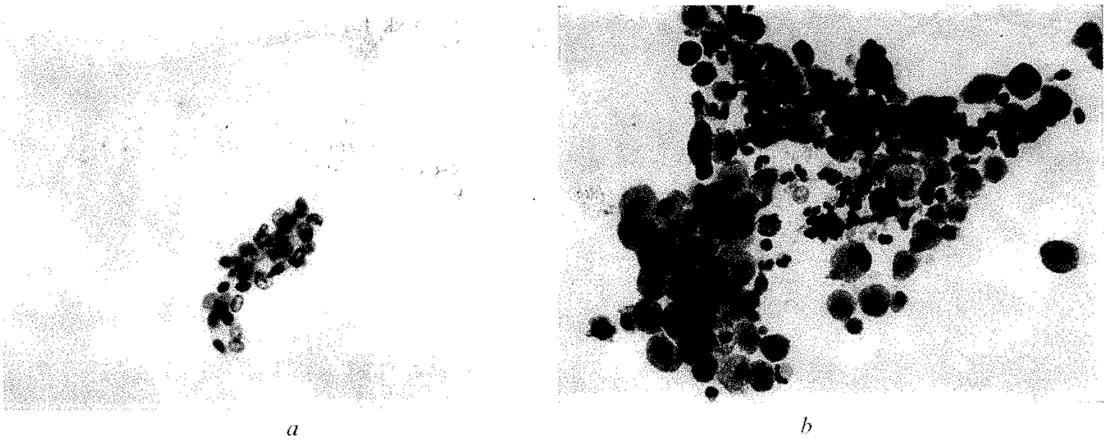
a *b*

Fig. 3. Non-malignant cells seen in cyst aspirates: (*a*) probably epithelial; (*b*) foamy macrophages with polymorphs. (HE. ×390.)

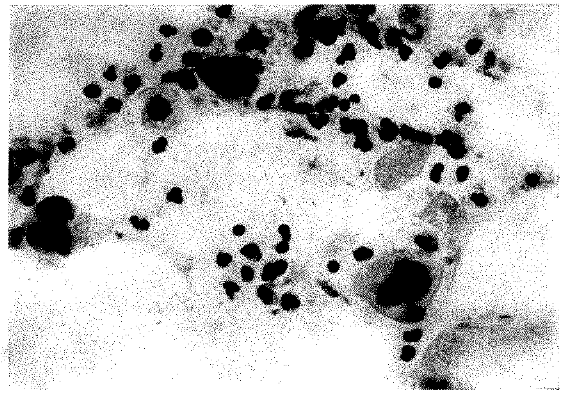

Fig. 4. Large, bizarre cells from squamous carcinoma with pus cells. (HE. ×390.)

Patients and methods

A prospective study was undertaken from November 1970 to December 1976. Patients were attending the surgical out-patients' clinic at the General Infirmary at Leeds and the majority were attending one unit, i.e. the Combined Breast Clinic. Patients whose lesions were diagnosed as breast cysts were treated by needle aspiration, without local anaesthetic (*Fig.* 2). Each cyst was aspirated as completely as possible and the fluid sent in a clean, dry, sterile bottle to the pathology department where it was received within 2 h. The fluid was then centrifuged for 5 min at 1500 rev/min (MSE Super Minor Centrifuge), the supernatant was pipetted off and the sediment then smeared on to a slide which was fixed in 50/50 ether alcohol or pure absolute alcohol. The slide (which was never allowed to become dry) was then stained with haematoxylin and eosin and the smear mounted with a cover slip as for conventional histology. Typical smears of breast cyst contents are seen in *Fig.* 3.

Results

In general, a few cells were found in the cyst smears. Most were recognized as epithelial cells or histiocytes and occasionally numerous pus cells were present. The results are shown in *Table I*. Three hundred and forty-eight specimens were obtained from 215 patients (some being repeat aspirations in the same patient) and in 1 case positive cytology was obtained (*Fig.* 4), though there were 9 'suspicious' reports. Three hundred and thirty-eight specimens contained either benign or no cells. The single patient with positive cytology did indeed have a breast carcinoma, though this was not intracystic but a squamous carcinoma that had become necrotic centrally.

Table I: SUMMARY OF NUMBERS OF PATIENTS AND SPECIMENS IN THE SURVEY TOGETHER WITH THEIR CYTOLOGY REPORTS AND THE RESULTS OF FOLLOW-UP

	No. of patients	No of specimens	Report		
			+ve	Suspect	−ve
Totals	215	348	1	9	338
Cases lost to follow-up	37	54	0	1	53
Cases followed up	178	294	1*	8†	285‡

Result of follow-up: * Positive confirmed. † None had or developed a new growth. ‡ Four had or developed breast cancer.

Although we had failed to detect cancer at initial presentation in the vast majority of these women it was just conceivable that a neoplastic lesion might have been missed, and for this reason as many of these patients as possible were followed up. Thirty-seven patients were lost to follow-up, leaving a total of 178 for study over a period of up to 7 years. Eight of the 9 suspicious cases were followed and none developed a carcinoma, 5 of these also have negative biopsies. The 1 suspicious case was lost to follow-up but we have no reason to believe (because of referral patterns in Leeds) that this patient developed a carcinoma. Four patients with negative cytology, however, were subsequently proved to have breast carcinoma. In 2 of these cases, on immediate follow-up a lump persisted after aspiration and in both cases a carcinoma was found at the site of the lump, i.e. their carcinomas had been clinically unmasked by decompression of coexisting breast cysts. In the other 2 cases the patients developed a carcinoma in the same breast as the cyst, one at 4 and the other at 7 years after aspiration. In our opinion these cases could hardly be considered false negatives.

Discussion

Once a cytology service is established surgeons will tend to send samples to it without necessarily critically examining its usefulness. However, Forrest et al.

(1975), are of the opinion that breast cyst cytology is useful, since out of 149 cysts aspirated by them, abnormal findings in 36 patients led to excision of the cyst, revealing carcinoma in 4 cases. This yield was significantly higher than ours. Others have also reported a higher incidence of cancer associated with cysts than we experienced; Patey and Nurick (1953) found 8 carcinomas associated with 76 cysts and Rosemond et al. (1955) reported 2 carcinomas associated with 140 cysts. As we have indicated previously, intracystic carcinoma is in itself extremely rare and it seems a futile exercise to hope to recognize such growths by routine cytology. Furthermore, since there is no definite relationship between fibrocystic disease and breast cancer, needle aspiration of cysts in fibrocystic disease is not likely to be particularly rewarding. Gaspar (1961) reviewed 15 surveys of breast cyst aspiration studies, including his own, and his conclusion was that 'As Papanicolaou examination of breast cyst fluid is unrewarding, this procedure has been abandoned.' His review included a total of 1364 patients with breast cysts, 12 of whom had cancers. In 4 cases these carcinomas were associated with cysts, in a further 4 patients these occurred in the same breast but not in the cyst and in the remaining 4 they occurred in the contralateral breast. Small surveys are reported by Roth et al. (1977) and Van Bogaert and Mazy (1977) in which 72 cysts were aspirated and all were negative cytologically. A recent large survey is that of Rosemond et al. (1977), who had only 3 cancers in 3000 cyst aspirates and therefore concluded that cytology is unnecessary.

From our own experience, we have confirmed that needle aspiration of breast cysts is a safe and reliable method of treatment. We conclude that there is nothing to be gained by routinely submitting breast cyst fluid for cytology, since the risk of missing a carcinoma is very small, particularly if the following clinical protocol is obeyed: Recommend biopsy if (*a*) *aspiration fails*, i.e. the lump may be solid, or (*b*) the lump recurs after *re-examination at 1 month*, if mammograms indicate the necessity. Routine cytology is therefore not only unnecessary but wasteful of time and resources. In this series we were interested to note that 4 of the 178 patients with negative cytology either had (2 cases) or subsequently developed (2 cases) a carcinoma. This does not appear to indicate an appreciable risk for patients with fibrocystic disease and we believe that this is generally the experience of others.

Finally, we would reiterate the general clinical rules for follow-up in patients in whom cysts are aspirated. It is most important after aspiration of a cyst that careful re-examination of the breast at the time and again 4 weeks later is carried out. Should a lump persist or recur we believe that mammography is indicated and a decision is then taken as to whether repeat aspiration or excision biopsy should be undertaken.

References

ATKINS H. (1952) Pain in the breast. *Lancet* **1**, 271–274.

FORREST A. P. M. (1974) Primary cancer of the breast: indication for therapy. In: ATKINS H. (ed.) *The Treatment of Breast Cancer*. Lancaster, MTP, p. 32.

FORREST A. P. M., KIRKPATRICK J. R. and ROBERTS M. M. (1975) Needle aspiration of breast cysts. *B. Med. J.* **3**, 30–31.

GASPAR M. R. (1961) Aspiration of breast cysts. *Calif. Med.* **95**, 227–231.

GATCHELL F. C., DOCKERTY M. B. and CLAGETT O. T. (1958) Intracystic carcinoma of the breast. *Surg. Gynecol. Obstet.* **106**, 347–352.

KALISHER L. (1977) Intracystic carcinoma of the breast. *Breast* **3**, 32–33.

KEYNES M. (1966) Lumps in the breast. (Letter to the Editor.) *Br. Med. J.* **2**, 235.

PATEY D. H. and NURICK A. W. (1953) Natural history of cystic disease of the breast treated conservatively. *Br. Med. J.* **1**, 15–17.

RIMSTEN A., STENKVIST B., JOHANSON H. et al. (1975) The diagnostic accuracy of palpation and fine-needle biopsy and an evaluation of their combined use in the diagnosis of breast lesions. *Ann. Surg.* **182**, 1–8.

ROSEMOND G. P., BURNETT W. E., CASWELL H. T. et al. (1955) Aspiration of breast cysts as a diagnostic and therapeutic measure. *Arch. Surg.* **71**, 223–229.

ROSEMOND G. P., MAIER W. P. and BROBYN T. J. (1977) Needle aspiration of breast cysts. *J. Family Practice* **4**, 1157–1160.

ROTH J. A., FEINBERG M. and MCAVOY J. M. (1977) Carcinoma arising in the wall of a breast cyst during pregnancy. *Ann. Surg.* **185**, 247–250.

SCHNUG E. G. and CAVANAGH C. R. (1966) Aspiration in the management of recurrent cysts of the breast. *Surg. Gynecol. Obstet.* **122**, 355–357.

VAN BOGAERT L. G. and MAZY G. (1977) Reliability of the cyto-radio-clinical triplet in breast pathology diagnosis. *Acta Cytol.* **21**, 60–62.

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Spontaneous rupture of a liver cell adenoma after long term methyltestosterone: report of a case successfully treated by emergency right hepatic lobectomy

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SUMMARY

A case of spontaneous rupture of a liver cell adenoma is reported in a female transexual treated with methyltestosterone 150 mg daily for 7 years. Emergency right hepatic lobectomy was performed successfully. Histology showed peliosis hepatis also.

Emergency resection of a liver cell adenoma has been reported in a young woman taking oral contraceptives, and an elective resection in another female transexual treated with methyltestosterone. However, to the best of our knowledge this is the first case of emergency resection of a spontaneously ruptured liver cell adenoma in a transexual treated with long term methyltestosterone. Since there are numerous other patients similarly treated, it may be expected that this complication will be seen again.

Case report

A 39-year-old female-to-male transexual was admitted as a surgical emergency. He had been treated with methyltestosterone 150 mg daily for the past 7 years, and had undergone bilateral subcutaneous mastectomy, hysterectomy and bilateral salpingo-oophorectomy. He had previously borne a child. Whilst on holiday he experienced a gradual onset of constant abdominal pain, which after 48 h became severe and radiated to the right scapular region. On examination he was well built, tanned, muscular, bearded, with profuse body hair of male distribution, but had female genitalia and an enlarged clitoris. He was febrile (38 °C) and in pain, with a sinus tachycardia of 115/min. The abdomen was slightly distended, with generalized tenderness and guarding, most marked in the right upper quadrant. The upper abdomen was dull to percussion, filled by an ill-defined mass, but the liver and spleen were not palpable. Bowel sounds were present and rectal examination was normal.

Investigations showed Hb 7·4 g/dl, WBC 27·6 × 10^9/l, blood urea 19·7 mmol/l, bilirubin 39 mmol/l, alkaline phosphatase 213 mU/ml, LDH greater than 608 mU/ml, SGOT greater than 253 mU/ml and amylase 255 U/l. Abdominal X-rays showed an opaque mass filling the entire right upper quadrant.

Laparotomy revealed a copious stale haemoperitoneum for which initially no cause could be found, but eventually a ragged split some 15 × 10 cm was felt in the most posterior part of the dome of the *right* hepatic lobe, which was greatly enlarged and softened and appeared to contain a large, friable, pale-red mass. The spleen was of normal size, and there was no evidence of portal hypertension.

The incision was extended into the right chest, and as it seemed that the bleeding could be controlled in no other way, a right hepatic lobectomy was performed. The common bile duct was not drained, several large peritoneal drains were inserted and broad spectrum antibiotics, 10 per cent dextrose and salt-poor albumin were given for several days. Postoperative recovery was uneventful, and the serum glucose and albumin, platelet counts and clotting profiles all remained within the normal ranges.

Pathological examination of the resected lobe revealed an ill-defined mass occupying most of the resected lobe. The mass was haemorrhagic and slightly paler than normal liver, but not clearly demarcated from it. Histologically the tumour was a liver cell adenoma composed of normal-looking liver cells arranged in irregular plates and separated by sinusoids. Portal tracts were absent. The appearances were id[illegible] those reported by Paradinas et al. (1977). In ad[illegible]ous thickened blood vessels were present, and the [illegible] many areas of necrosis and haemorrhage, the latter filling cavities not lined by epithelium. The histological appearances were those of peliosis hepatis and liver cell adenoma.

Discussion

17-Alpha-alkylated androgenic–anabolic steroids such as methyltestosterone may cause abnormalities of the standard liver function tests, which revert to normal if the drug is stopped (Foss and Simpson, 1959). Carbone et al. (1959) studied 17 patients with normal liver function given methyltestosterone 67 mg per day. At the end of 3 weeks 40 per cent showed elevation of plasma SGOT and 90 per cent showed BSP retention greater than 6 per cent 45 min after injection.

Methyltestosterone and oxymetholone may cause cholestatic jaundice, but this is an unusual complication (Wynn et al., 1961). Although 60 per cent of patients showed elevated SGOT after a 3–5-week course of norethandrolone (60 mg daily), needle biopsy revealed cholestasis in only 15 per cent (Schaffner et al., 1959).

17-Alpha-alkylated steroids have been implicated in the development of liver tumours—which have been variously described as hepatic adenoma (Recant and Lacy, 1965; Bruguera, 1975; Westaby et al., 1977), or hepatocellular carcinoma (Dosik et al., 1970; Bernstein et al., 1971; Johnson et al., 1972)—since they have been used in all the well-documented cases. This group includes oxymetholone and methyltestosterone. It is uncertain if any of these tumours were truly malignant in that neither alpha-fetoprotein production nor metastasis was documented satisfactorily (Anthony, 1975). Paradinas et al. (1977) have decribed the morphological changes in detail, and suggested that a single pathological process (hyperplasia, related perhaps to the anabolic effects of methyltestosterone) could be responsible for both peliosis, through mechanical obstruction of hepatic veins, and the formation of nodules and tumours.

Peliosis hepatis is a benign condition of the liver of unknown aetiology, characterized by a diffuse angiomatoid change, with minute spaces of haemorrhagic appearance (Yanoff and Rawson, 1964). Peliosis hepatis has been reported after the use of norethandrolone, oxymetholone and methyltestosterone (Gordon et al., 1960; Bernstein et al., 1971; Westaby et al., 1977). In 1974 Bagheri and Boyer described 7 cases of peliosis hepatis in patients treated with anabolic–androgenic steroids. Two developed intraperitoneal

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haemorrhage and died. At autopsy in each case rupture of the *diaphragmatic* surface of the *right* lobe of the liver was found. In both cases, therefore, the site of rupture was the same as in our case, in a surgically 'difficult' place.

The connection between oral contraceptives and hepatic tumours, first reported by Baum et al. (1973), has been recently discussed by Vana et al. (1977). Of 543 liver tumours of all types in the USA, 96 were liver cell adenomas. In 11 of these (11·5 per cent), intraperitoneal haemorrhage occurred, and 8 of these 11 patients died (73 per cent). When a liver cell adenoma ruptures and presents with haemoperitoneum, the mort[illegible] has been quoted as 60 per cent (Davis et a[illegible] We have found no report in the world literature of emergency hepatic resection performed for spontaneous rupture of the liver after long term methyltestosterone. Elective right hemihepatectomy for a large liver cell adenoma after the use of long term methyltestosterone has been reported by Westaby et al. (1977), and emergency extended right lobectomy for haemorrhage from an adenoma in a young woman taking oral contraceptives was described by Bein and Goldsmith (1977).

Our patient is one of the series of 60 patients treated with long term methyltestosterone 150 mg daily by Westaby et al. (1977). Eighteen were impotent males and 42 were female transexuals. Since treatment in transexuals must be life-long, further cases such as ours may be expected. It is to be hoped that virilizing drugs other than 17-alpha-alkylated steroids can be used.

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References

ANTHONY P. P. (1975) Hepatoma associated with androgenic steroids. *Lancet* **1**, 685–686.

BAGHERI S. A. and BOYER J. L. (1974) Peliosis hepatis associated with androgenic–anabolic steroid therapy: a severe form of hepatic injury. *Ann. Intern. Med.* **81**, 610–618.

BAUM J. D., BOOKSTEIN J. J., MOLTZ F. et al. (1973) Possible association between benign hepatomas and oral contraceptives. *Lancet* **2**, 926–928.

BEIN N. N. and GOLDSMITH H. S. (1977) Recurrent massive haemorrhage from benign hepatic tumours secondary to oral contraceptives. *Br. J. Surg.* **64**, 433–435.

BERNSTEIN M. S., HUNTER R. L. and YACHNIN S. (1971) Hepatoma and peliosis hepatis developing in a patient with Fanconi's anaemia. *N. Engl. J. Med.* **284**, 1135–1136.

BRUGUERA M. (1975) Hepatoma associated with androgenic steroids. *Lancet* **1**, 1295.

CARBONE J. V., GRODSKY G. M. and HJELLE V. (1959) Effect of hepatic dysfunction on circulating levels of sulphobromophthalein and its metabolites. *J. Clin. Invest.* **38**, 1989–1995.

DAVIS M., PORTMANN B., SEARLE M. et al. (1975) Histological evidence of carcinoma in a hepatic tumour associated with oral contraceptives. *Br. Med. J.* **4**, 496–498.

DOSIK H., HSU L. U., TODARO G. J. et al. (1970) Leukaemia in Fanconi's anaemia: cytogenetic and tumour virus susceptibility studies. *Blood* **36**, 341–352.

FOSS G. L. and SIMPSON S. L. (1959) Oral methyltestosterone and jaundice. *Br. Med. J.* **1**, 259–263.

GORDON B. S., WOLF J., KRAUSE T. et al. (1960) Peliosis hepatis and cholestasis following administration of norethandrolone. *Am. J. Clin. Pathol.* **33**, 156–165.

JOHNSON F. L., FEAGLER J. R., LERNER K. G. et al. (1972) Association of androgenic–anabolic steroid treatment with development of hepatocellular carcinoma. *Lancet* **2**, 1273–1276.

PARADINAS F. J., BULL T. B., WESTABY D. (1977) Hyperplasia and prolapse of hepatocytes into hepatic veins during long term methyltestosterone therapy: possible relationships of these changes to the development of peliosis hepatis and liver tumours. *Histopathology* **1**, 225–246.

RECANT L. and LACY P. (1965) Fanconi's anaemia and hepatic cirrhosis. *Am. J. Med.* **39**, 464–475.

SCHAFFNER F., POPPER H. and CHESROW E. (1959) Cholestasis produced by the administration of norethandrolone. *Am. J. Med.* **26**, 249–254.

VANA J., MURPHY G. P., ARONOFF B. L. (1977) Primary liver tumours and oral contraceptives. *JAMA* **238**, 2154–2158.

WESTABY D., OGLE S. J., PARADINAS F. J. et al. (1977) Liver damage from long term methyltestosterone. *Lancet* **2**, 261–263.

WYNN V., LANDON J. and KAWERAU E. (1961) Studies of hepatic function during methandienone therapy. *Lancet* **1**, 69–75.

YANOFF M. and RAWSON A. J. (1964) Peliosis hepatis, anatomic study with demonstration of two varieties. *Arch. Pathol.* **77**, 159–165.

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Haematogenous osteomyelitis of the metatarsal sesamoid

I. J. CARTLIDGE AND W. J. GILLESPIE*

SUMMARY

A case of haematogenous osteomyelitis of the medial first metatarsal sesamoid is presented and the differential diagnosis discussed. Review of the literature suggests that the condition is rarely seen and tends to present in childhood and adolescence. This contrasts with metatarsal sesamoid osteomyelitis due to direct spread of infection, which occurs in the elderly as an important complication of the diabetic foot.

HAEMATOGENOUS osteomyelitis of the first metatarsal sesamoids was authoritatively reported for the first time by Bennet in 1935, although Lange's case (1928) of 'typical sesamoiditis' progressed to suppuration and sequestration and was probably osteomyelitis.

Smith (1941) contributed the first case in the British literature, since which time a further 6 patients with haematogenous staphylococcal osteomyelitis of the sesamoid have been recorded (Rowe, 1963; Colwill, 1969; Torgerson and Hammond, 1969).

The 2 patients described by Gordon et al. (1974) with *Pseudomonas aeruginosa* as the infecting organism had sesamoid osteomyelitis due to direct spread from a penetrating wound, while the second of the 2 cases reported by Torgerson and Hammond (1969) was that of a diabetic with deep spread of infection from an ulcerated plantar callus in a neuropathic foot.

Such cases are not rare. Over a period of 2 years until September 1977, 14 patients were seen in the Diabetic Outpatient Department at the Royal Infirmary, Edinburgh, with significant skin breakdown in the plantar aspect of the first metatarsal head. Of these, there were 3 definite cases of sesamoid osteomyelitis confirmed by radiography, and 2 others, in whom amputation had been performed for irreversible ischaemia, where preoperative radiographs suggested infective resorption of the sesamoids in addition to the adjacent first metatarsal head (Paterson, 1977).

The comparative rarity of the haematogenous variety of sesamoid infection prompts the following report of the only recorded case in the Edinburgh Orthopaedic Unit over the past 5 years.

Case report

P. F., a 15-year-old schoolboy, presented to the Orthopaedic Unit on 9 November 1976 with a 1-month history of intermittent throbbing pain and swelling on the medial and plantar aspects of the first left metatarsal head, only transiently helped by prescriptions of erythromycin and of aspirin. Up until the onset of the pain, he had been active in rugby union football, but could describe no specific precipitating trauma.

At the time of presentation, he had great pain on weight bearing, with tenderness, marked erythema and swelling on the medial aspect of the foot, associated with an area of blistering on the plantar aspect of the first metatarsophalangeal joint. He was afebrile and free of lymphangitis or lymphadenopathy, but the white cell count was 9·3 × 10^9/l with a neutrophil leucocytosis, and ESR was raised at 51 mm in the first hour (Westergren). Plasma glucose was normal, titres against staphylococci and streptococci were not raised, and no agglutinating antibodies to brucella or salmonella strains were detected. Radiographic evidence [illegible] nsidered at the time to show some rarefaction of the base [illegible] the proximal phalanx of the great toe, in comparison with a film availa[illegible] month previously at the onset of symptoms (*Fig.* 1).

No other abnormality was det[illegible] the medial sesamoid was bipartite, and, in retrospect, it is clear that the degree of separation of the parts of the sesamoid had increased in the month preceding orthopaedic presentation. Aspiration of the infected area produced no pus, but two drops of sanguinous fluid were cultured and grew coagulase-positive *Staphylococcus aureus*. A diagnosis of osteomyelitis, either in the proximal phalanx or in the metatarsal head, having been made, the left foot was kept in a plaster slipper for 2 weeks, and flucloxicillin given for 8 weeks, with resolution of physical signs and only very minor residual discomfort on weight bearing.

Radiographs taken on 29 November 1976 (*Fig.* 2) and 17 January 1977 (*Fig.* 3), however, showed increasing fragmentation of the distal component of the bipartite medial sesamoid, with migration away from the proximal component. These features were initially unrecognized. By 28 February 1977 a sinus had developed, opening on the medial aspect of the head of the first left metatarsal, without systemic upset or restriction of joint movement but producing pus with large numbers of *S. aureus* and showing three calcific fragments of sesamoid in the sinus track on X-ray examination (*Fig.* 4).

Osteomyelitis of the medial sesamoid was diagnosed, and further rest and flucloxacillin prescribed in the expectation of spontaneous extrusion of bony fragments, but little improvement followed and the sinus track with its contained sequestra was excised *in toto* on 24 March 1977. Histology, in addition to confirming the diagnosis, revealed a vigorous tenosynovitis in the adjacent fibres of the flexor hallucis brevis tendon. Healing was complete within 3 weeks and follow-up at 1 year after presentation indicated complete cure.

Conclusion

The delay in clinical diagnosis and in interpretation of radiological signs and the late sequestration are characteristic of the condition described, and have been discussed, in particular, by Rowe (1963) and Colwill (1969). It seems that we are slow to learn. Few cases of haematogenous sesamoid osteomyelitis are seen. Nearly all those reported have been in children and adolescents and in this age group it assumes relative importance as a consequence of the rarity of other conditions in the differential diagnosis. Osteomyelitis (White and Dennison, 1952), primary septic arthritis (Borrella et al., 1963), gonococcal arthritis (Fink, 1965) and tuberculous arthritis (Harris and Coulthard, 1942) are all unusual in the forefoot. Gout and pseudogout are extremely rare in the first two decades (Hollander, 1972) and the former has been reported only in association with rare specific syndromes (Riley, 1960; Decker and Vandeman, 1962; Lesch and Nyhan, 1964). Juvenile rheumatoid arthritis and rheumatic fever seldom present affecting single small joints.

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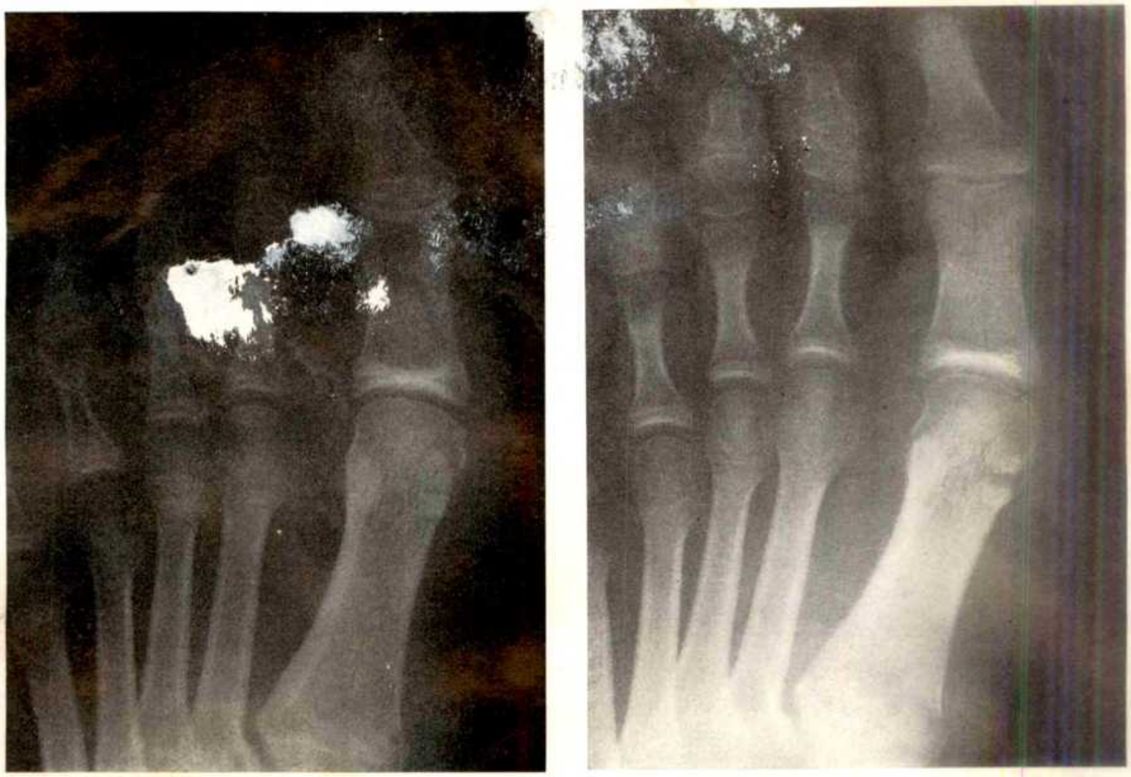

a *b*

Fig. 1. *a*, Anteroposterior view of left forefoot on 12 October 1976; *b*, anteroposterior view on November 1976.

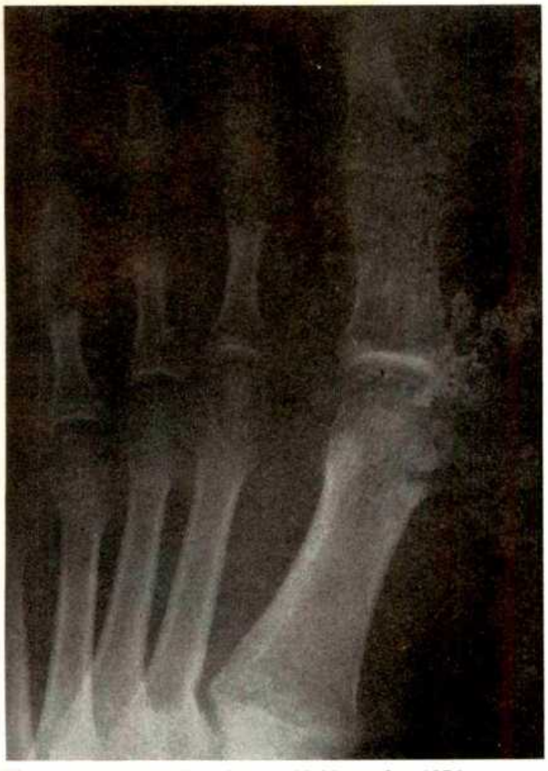

Fig. 2. Anteroposterior view on 29 November 1976.

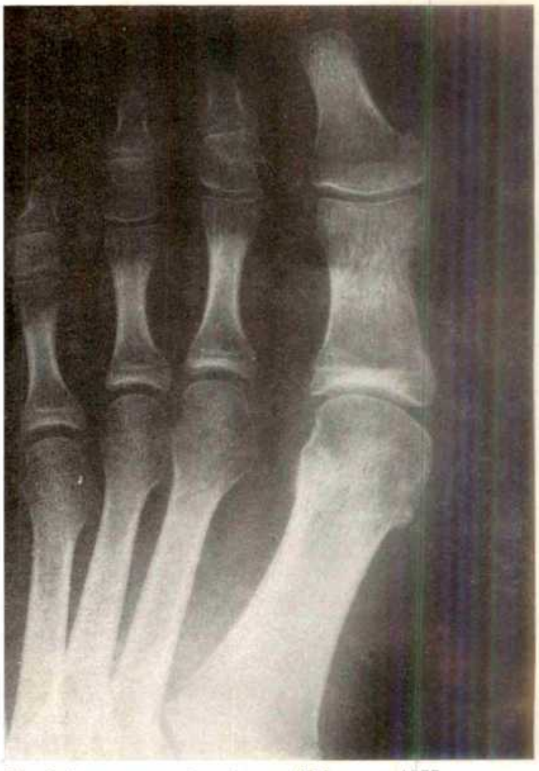

Fig. 3. Anteroposterior view on 17 January 1977.

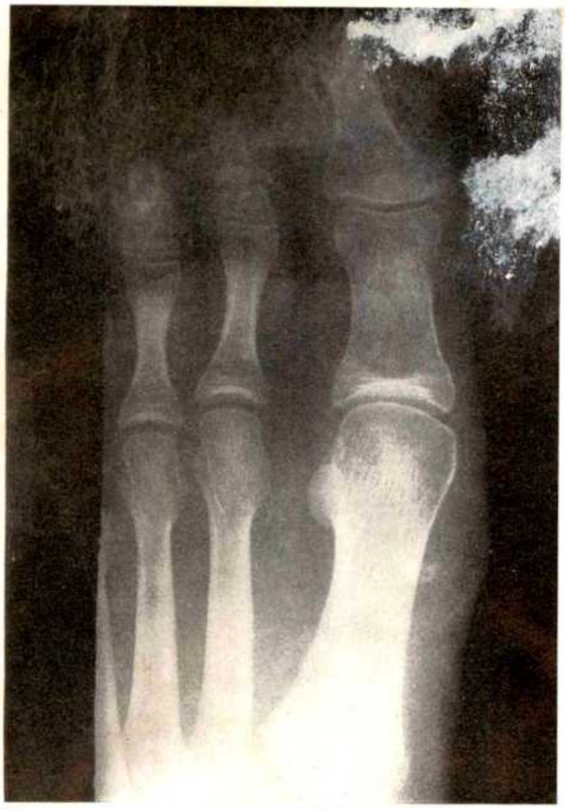

Fig. 4. Anteroposterior view on 28 February 1977.

Suspicion should therefore be aroused in a young patient with acute first metatarsalgia. Careful radiological examination of the sesamoids has a high probability of establishing the diagnosis. Whether or the natural history of the condition is affected by earlier diagnosis, appropriate counselling of the patient and the parents should be possible at an early stage.

References

BENNET K. (1935) Septische Osteomyelitis als Ätiologie der sog. Typischen Erkrankung [illegible] Sesambeine des I. Metatarsal- [illegible] *Acta Chir. Scand.* **76**, 103.

[illegible]LA [illegible] et al. (1963) Septic arthritis in childhood. *J. Pediatr.* **62**, 742–747.

COLWILL M. (1969) Osteomyelitis of the metatarsal sesamoids. *J. Bone Joint Surg.* **51B**, 464–468.

DECKER J. L. and VANDEMAN P. R. (1962) Renal calculi preceding gouty arthritis in a child. *Am. J. Med.* **32**, 805–810.

FINK C. W. (1965) Gonococcal arthritis in children. *JAMA* **194**, 237–238.

GORDON S., EVANS E. and GREER R. (1974) Pseudomonas osteomyelitis of the metatarsal sesamoid of the great toe. *Clin. Orthop.* **99**, 188–189.

HARRIS R. I. and COULTHARD H. S. (1942) Prognosis in bone and joint tuberculosis. *J. Bone Joint Surg.* **24**, 382–395.

HOLLANDER J. L. (1972) *Arthritis and Allied Conditions*, 8th ed. Philadelphia, Lea & Febiger, pp. 904, 948.

LANGE M. (1928) Die typische Sesambeinerkrankung des I. Metatarsal-Knochens mit Ausgang in Vereiterung. *Zeit. Orthop. Chir.* **49**, 595.

LESCH M. and NYHAN W. L. (1964) A syndrome consisting of hyperuricaemia, mental retardation, choreo-athetosis and self-destructive biting. *Am. J. Med.* **36**, 561–563.

PATERSON R. (1977) Personal communication.

RILEY I. D. (1960) Gout and cerebral palsy in a three-year-old boy. *Arch. Dis. Child.* **35**, 292–295.

ROWE M. (1963) Osteomyelitis of metatarsal sesamoid. *Br. Med. J.* **1**, 1071–1072.

SMITH R. (1941) Osteitis of the metatarsal sesamoid including a case report of acute pyogenic osteomyelitis. *Br. J. Surg.* **29**, 19–22.

TOGERSON W. and HAMMOND G. (1969) Osteomyelitis of the sesamoid bones of the first metatarso-phalangeal joint. *J. Bone Joint Surg.* **51A**, 1420–1422.

WHITE M. and DENNISON W. M. (1952) Acute haematogenous osteitis in childhood. *J. Bone Joint Surg.* **34B**, 608–623.

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Correspondence

Simple closure of perforated duodenal ulcers

Sir,
The article by M. J. Playforth and M. J. McMahon (*British Journal of Surgery*, **65**, 699–701) is an interesting summary of the experience at Leeds of simple closure of a perforated duodenal ulcer, but the authors' conclusions are surely totally unjustified. As they themselves point out, the information is entirely retrospective and in the absence of any figures at all for 'definitive' management of the first time perforated duodenal ulcer how can statements be made that 'the operation of simple suture of a duodenal ulcer is indicated only in young and middle-aged women' or 'our data do suggest that a lower operative mortality might result from the addition of a definitive procedure to closure of the perforation . . .' Presumably some information is available, since 62 of their patients had some form of management other than simple closure.

Personally I shall continue to oversew perforated duodenal ulcers unless there is a clear indication at the time of laparotomy that a complication may follow from not undertaking a definitive procedure, e.g. a second posterior chronic duodenal ulcer, or until a properly controlled prospective trial indicates results superior to those of the more major procedure. With careful postoperative follow-up those patients requiring subsequent definitive ulcer surgery can be selected, and in this respect it is interesting to note that six out of their eight 'ulcer-related complication' deaths occurred a considerable time (1–84 months) after simple closure.

M. H. JOURDAN

Department of Surgery
Guy's Hospital
London SE1 9RT

Sir,
The aim of our communication was to indicate that curative surgery for perforated duodenal ulceration (simple closure of the ulcer) carried a significant risk to life, due in part to the continued presence of the ulcer. It is common to find the tacit assumption that this procedure represents the baseline of safety in the management of perforating ulcers, and that more definitive measures confer the sole advantage that some patients will be spared a subsequent elective operation, albeit at the expense of an increased risk to health during the acute illness.

Thus, we were only concerned with those patients who actually underwent simple closure of the ulcer and did not wish to become embroiled in rather meaningless comparisons with the results from patients who had received a definitive procedure at the time of closure of their perforation. For the record, at the time of perforation closure, 2 patients received a partial gastrectomy and 20 a highly selective vagotomy, without mortality. Truncal vagotomy was carried out in 26 patients with 1 death (respiratory) and 14 were managed conservatively with 3 deaths. No complications resulting from the continued presence of an ulcer were seen in any of the patients who received an emergency definitive procedure. These patients clearly form a highly selected group and the results of their definitive treatment were predictably good.

As we pointed out in the paper, we were seeking evidence of disaster during follow-up. Incompleteness of the follow-up data was almost inevitable in a study of this type; more complete follow-up, however, could only *add* to the complications we found, and thus strengthen our case.

Personally, I would rather that my perforation, should it arise, *is* treated by a definitive procedure, carried out, needless to say, by a surgeon of my own choice.

M. J. MCMAHON

University Department of Surgery
The General Infirmary
Leeds

Abdominoperineal excision of the rectum

Sir,
Since 1964, when doing this operation I have commenced by cystoscopying the patient and passing retrograde ureteric catheters on each side.

This adds 20 min to the operation at the beginning, but I can assure you that it saves many more than 20 min during the operation, and I now take a delight in demonstrating to my assistant how he can find the ureters literally with his eyes shut!

I have been unable to find this procedure in any book on operative surgery and it may well be that it does not deserve mention. However, to those who have not employed it, I would recommend a try, if only for the saving of wear and tear on the surgeon's coronary vessels.

D. T. L. NASH

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Co. Down
Northern Ireland

Br. J. Surg. Vol. 66 (1979) 218–220

Book reviews

Advances in Surgery, Volume 11

Edited Charles Rob. 228 × 150 mm. Pp. 415 + xii. Illustrated 1977. London: Year Book Medical Publishers. £16·30.

THE eleventh volume of *Advances in Surgery* maintains the established policy of concise and comprehensive reviews of topics of current interest, and contains much of value for all surgical tastes. The recent impact of ultrasonography in the diagnosis of intra-abdominal lesions is acknowledged in a well-illustrated review, and, although not such a recent development, a section on microvascular surgery describes the more up-to-date applications in plastic and hand surgery, neurosurgery and urology. The more technical and 'craft' elements of surgery are covered by reviews of ulcerative colitis and Crohn's disease in the large bowel, the surgery of arterial embolism, injuries to metacarpal bones and joints and the use of adjuvant oncotherapy in the treatment of systemic micrometastases.

For those with interests in care of patients before and after operations there are chapters on hyperalimentation, monitoring of critically ill patients, problems with postoperative drug therapy and the respiratory distress syndrome. This book has, therefore, a little bit of succour for every surgeon who thirsts for something new and interesting.

The style of presentation is good and the factual content of each chapter is well judged; for example, the chapter on hyperalimentation by Joseph Fisher is over 60 pages in length but is essentially practical in the approach, describing techniques of administration and clinical application with a minimum of metabolic 'journalese' so that it remains intelligible to those who do not have a special interest. This is a worthwhile addition to the series of *Advances in Surgery*.

R. G. CLARK

Atlas of Surgery in the First Six Months of Life

S. Frank Redo. 245 × 195 mm. Pp. 188, with 300 illustrations. 1978. Maryland: Harper & Row. $27.50.

THIS atlas was conceived as a companion work to the volume entitled *Principle of Surgery in the First Six Months of Life* by the same author. The procedures commonly performed in the first 6 months of life are described. The operative techniques are clearly and concisely described and are well illustrated by halftone drawings. The technical details are supplemented by diagnostic and preoperative considerations and suggestions for postoperative management.

It was surprising to find a section on appendicectomy, a procedure rarely undertaken as such in the first 6 months. Moreover, some of the procedures and technical details are clearly out of date. In particular, I would mention duodenojejunostomy, which has been superseded by duodenoduodenostomy, a two-layer intestinal anastomosis which has virtually been abandoned in favour of a single-layer technique and open rectal biopsy has been replaced by the suction biopsy in all but a few selected cases. Oesophageal atresia repair by the entire extrapleural approach has resulted in a much improved mortality and morbidity rate when compared with the transpleural approach described by the author. The section on inguinal hernia in the male includes a description of inguinal herniorrhaphy. Most paediatric surgeons consider this unnecessary and limit the procedure to an inguinal herniotomy. A paramedian abdominal incision is preferred throughout. This is in contradistinction to the transverse incision used by most paediatric surgeons.

The cost of the atlas is £17·90 compared with £42·50 for the paediatric surgical volume edited by H. H. Nixon in the Operative Surgery series of Charles Rob and Lord Smith which is a much more comprehensive and valuable work.

L. SPITZ

Notebook of Medic[illegible]

[illegible] s prep[illegible] [illegible] postgraduates, but [illegible] clinical medical students. The first section [illegible] the usual range of endocrinology relate[illegible] surgery; the second section consists of ch[illegible] physiology, fetal physiology, perinatal and n[illegible]. Each chapter consists of a descriptive text in terse, not[illegible] with many charts and flow diagrams, followed by a number of multiple-choice questions based on the material presented and finally the key to the correct answers of the multiple-choice questions. The idea is that the student first refreshes [illegible] memory of previous reading and subsequently can test him[illegible] with the multiple-choice questions.

The real problem with this book is that it aims to cover the physiology of endocrinology at all levels from the medical student upwards. This means that a good portion of the book is too complicated for the medical student, and there are similar problems with regard to the material of gynaecological and obstetric interest compared with the material needed by surgeons and physicians. It seems likely that a student in any particular category may be reluctant to pay the cost of this book in order to cover only one small aspect of physiology, knowing that much of it would be inappropriate to his needs.

MICHAEL HORSLEY

Gynecologic and Obstetric Urology

Edited H. J. Buchsbaum and J. D. Schmidt. 260 × 180 mm. Pp. 461 + xiv. 1978. Philadelphia: Saunders. £24·00.

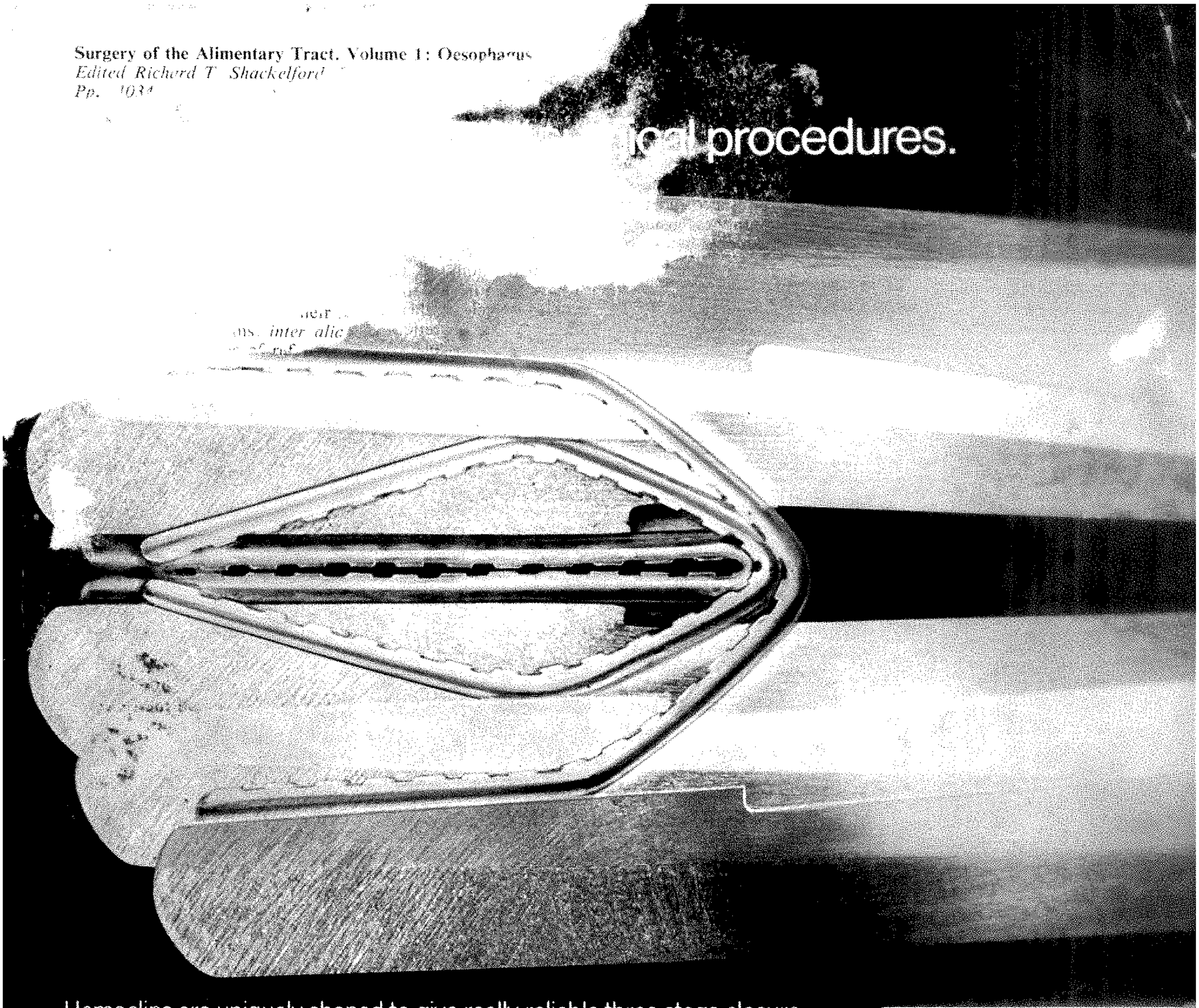
GYNAECOLOGISTS and urologists have for too long muttered threateningly about each other from opposite sides of the patient with a damaged ureter or misdiagnosed pelvic mass. This book reinforces the growing trend of reconciliation between these two specialties whose areas of interest are so close and who so often need each other's advice. The introduction to the book rightly deplores the inadequate training of gynaecologists in female urology and of urologists in gynaecology.

This multi-author textbook, originating from the Departments of Gynecology and Urology of the University of Iowa, aims to correct this defect. It is written particularly for the gynaecologist in training, 20 of its 31 authors being gynaecologists. The book starts with several excellent chapters on female genito-urinary embryology, anatomy and physiology. There follows a section of four chapters on the common urological problems met in gynaecological and obstetric surgery. These are short, well-written chapters with clear and useful diagrams. The third section, on various aspects of urinary incontinence and fistulas, includes no less than five separate chapters on operations to cure stress incontinence; most of the favourite operations are included but, unfortunately, some of the dogmatic statements only help to emphasize how little we really understand about urinary control mechanisms. There are then some comprehensive chapters on urinary tract infections and urinary tract involvement in gynaecological malignancy. Finally, there is an interesting section on the effect of pregnancy on renal function and the urinary tract.

It is not difficult for the individual surgeon to find favourite ideas and procedures omitted from this book, but for both the gynaecologist and urologist in training it can be thoroughly recommended as bridging the gap between these two specialties which have so many patients with problems common to them both.

EUAN MILROY

Surgery of the Alimentary Tract. Volume 1: Oesophagus
Edited Richard T Shackelford
Pp. 1034



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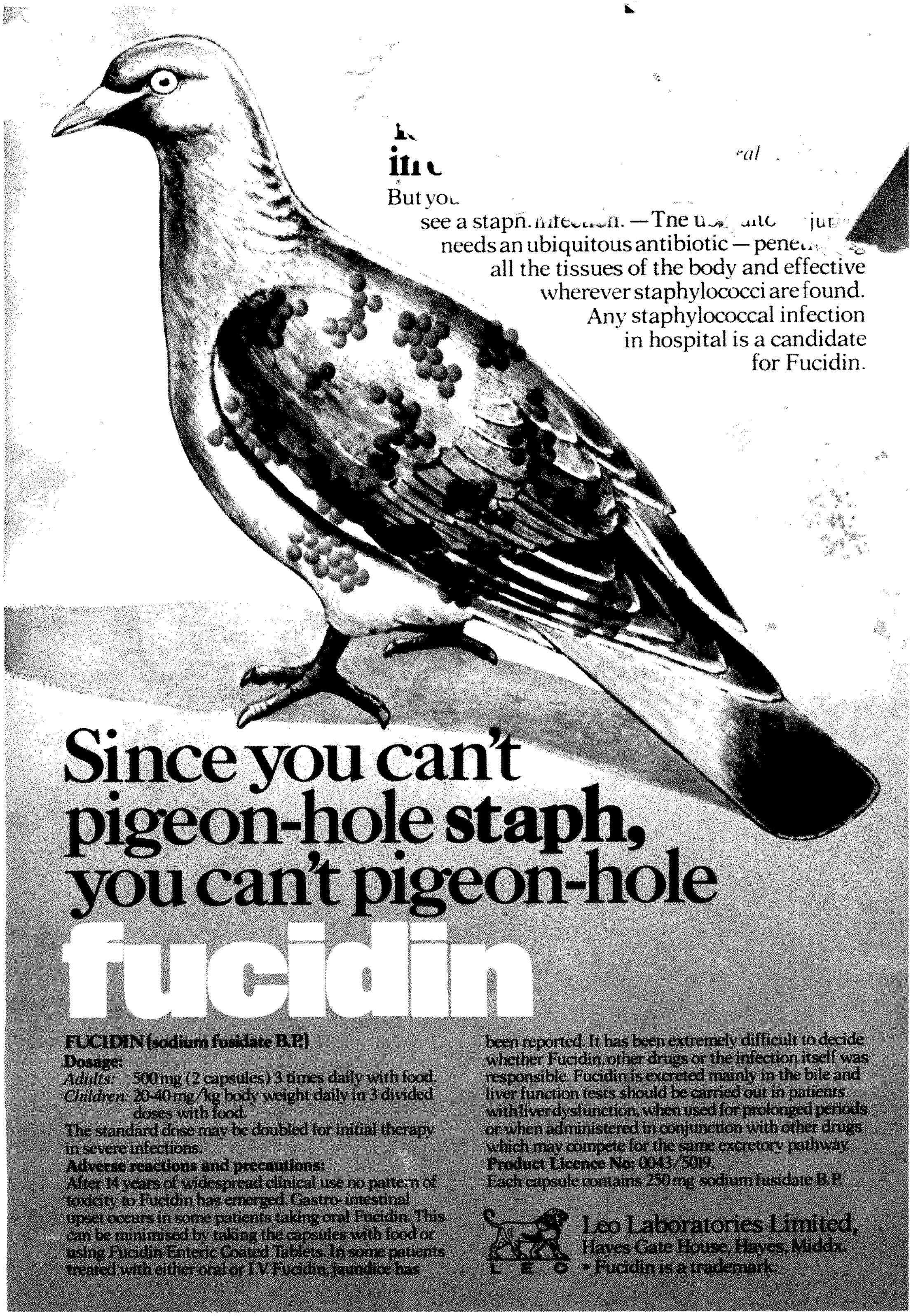

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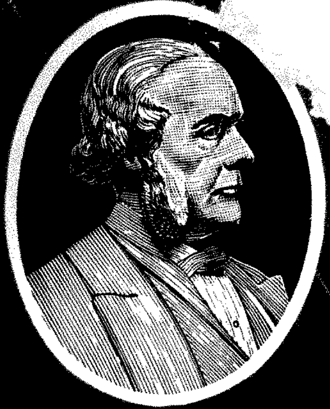

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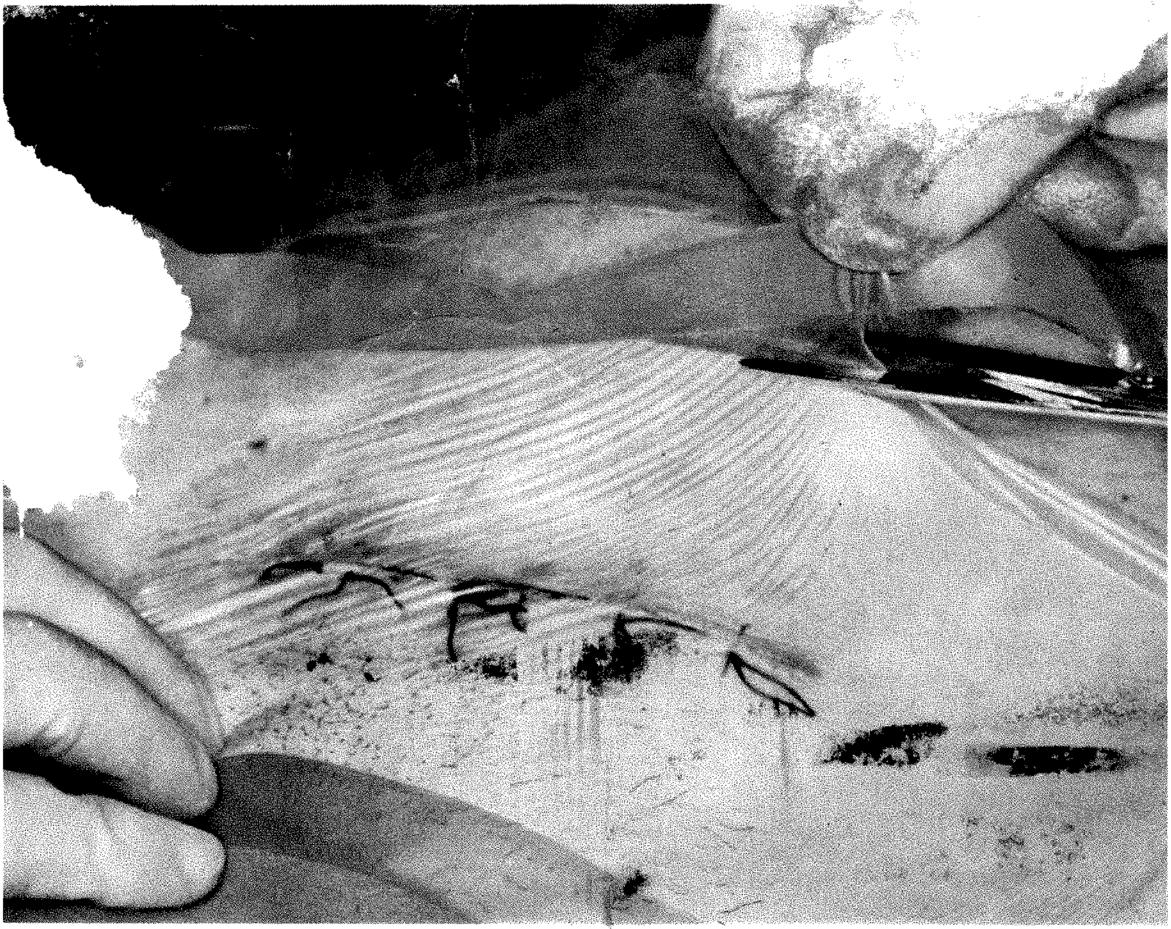

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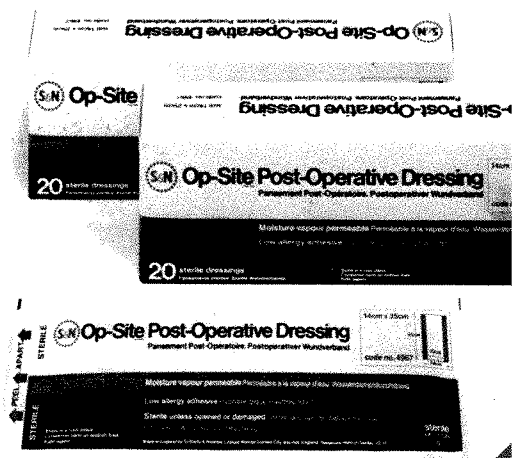
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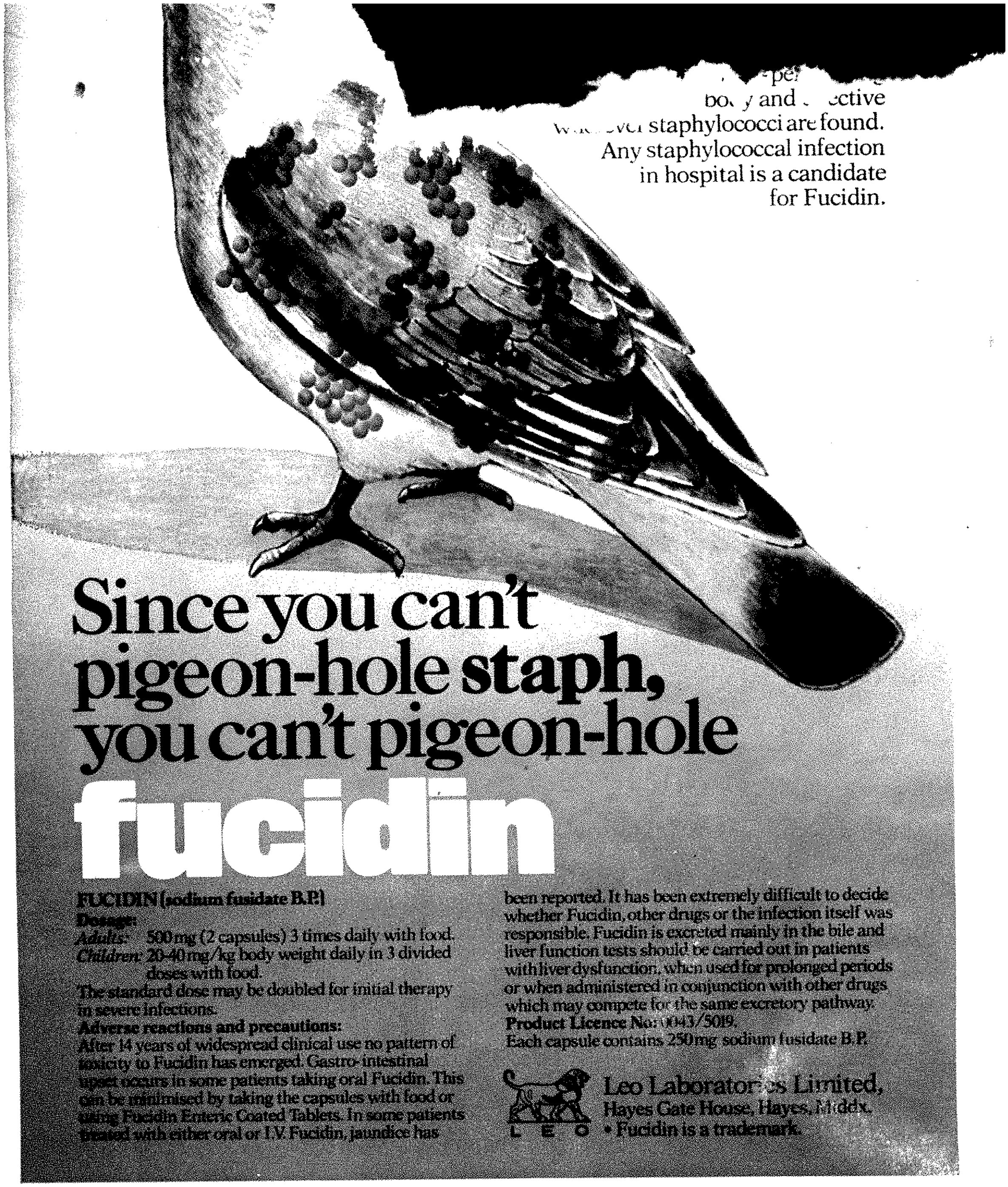

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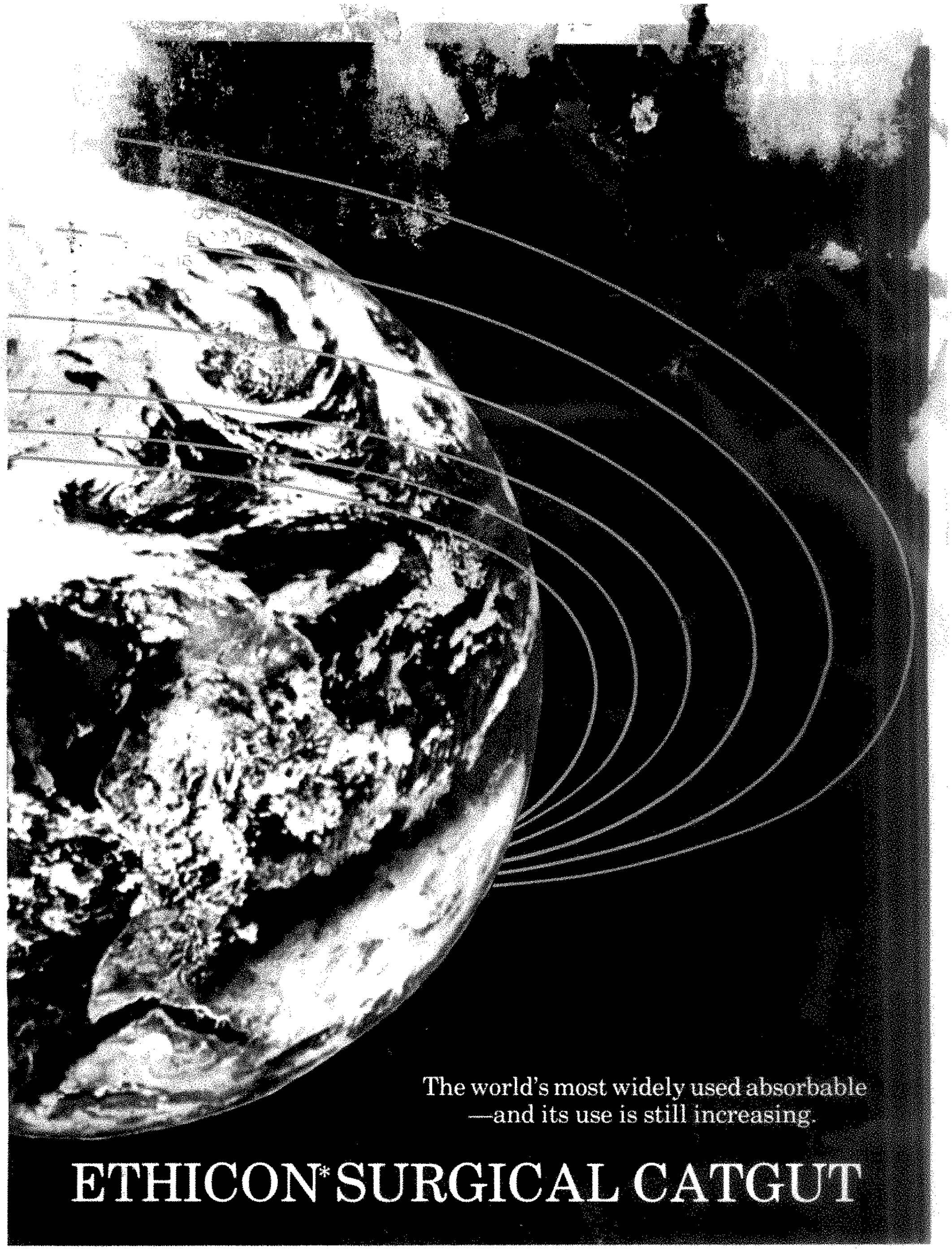
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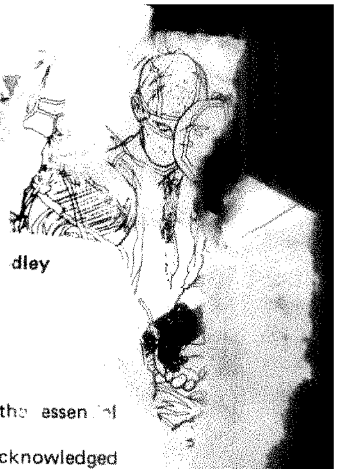

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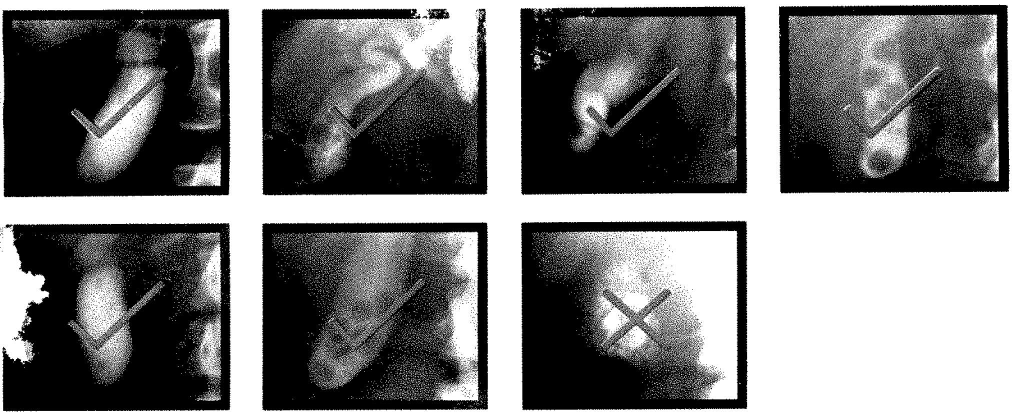

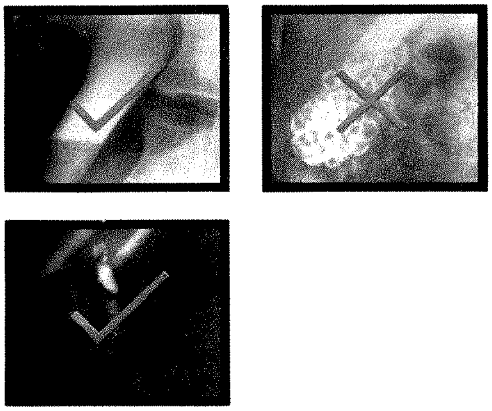

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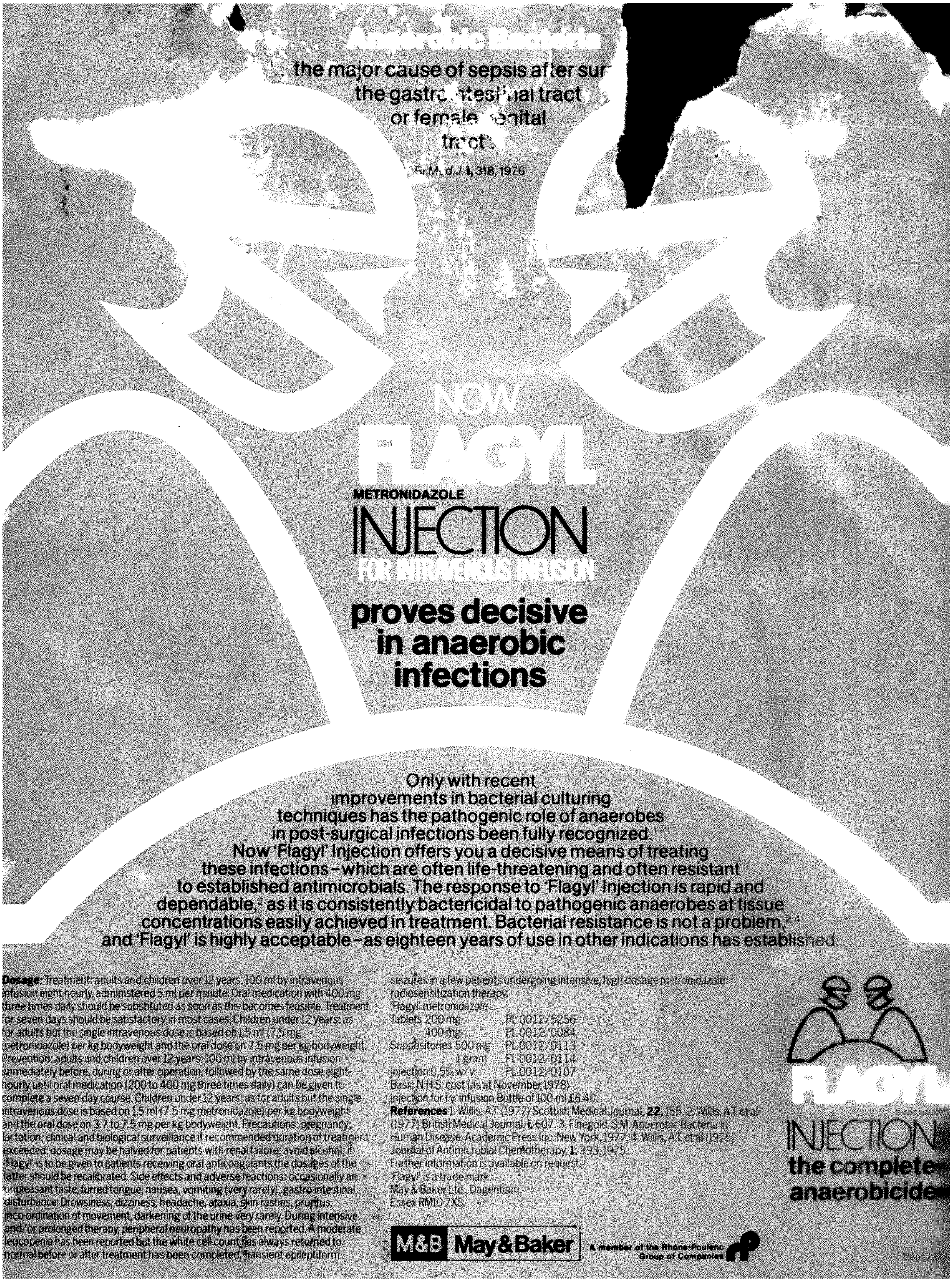

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Conservative surgery in reflux stricture of the oesophagus associated with hiatal hernia

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SUMMARY

During a 7-year period, 130 patients with oesophageal stricture resulting from long-standing reflux oesophagitis and hiatal hernia were referred for surgery. Eighty-seven of these patients underwent conservative surgery consisting of intraoperative transgastric retrograde dilatation combined with one of two types of anti-reflux operation: in 34 patients (group 1) an Allison-type operation for hiatal hernia was undertaken, and in the remaining 53 patients (group 2), a Nissen-type fundoplication was carried out. In 22 patients in this latter group the oesophagogastric junction could not be brought down into the abdomen in spite of extensive oesophageal mobilization and the fundoplication was finally placed above the diaphragm.

From the successful results in both groups (particularly in group 2), it is concluded that conservative surgery should be considered in cases of hiatal hernia with a reflux stricture that yields to intraoperative dilatation.

THE rational approach to the management of reflux oesophagitis with stricture involves the relief of the obstruction and the prevention of further gastro-oesophageal reflux that would otherwise cause recurrence of the stricture. Radical surgery involving excision of the stricture requires reconstruction of the upper alimentary tract using the stomach, jejunum or colon. This is inevitable in a number of cases but in many patients a more conservative approach may be employed.

This paper is a review of such a conservative approach in a personal series of patients treated over a period of 7 years. In the light of this, and a review of the literature, the place of conservative surgery in oesophageal stricture following reflux and hiatal hernia is discussed.

Patients and methods

In the past 7 years a total of 130 patients with long-standing hiatal hernia and reflux stricture was submitted to operation. Cases of oesophageal stricture without a demonstrable hiatal hernia are not included. Forty-three patients underwent resection of the stricture and reconstruction of the oesophagus. This group of patients is not presented here but is mentioned later in the discussion when appropriate. The remaining 87 patients underwent conservative surgery consisting of intraoperative dilatation of the stricture and an anti-reflux operation.

Patients were selected for conservative or radical surgery according to the following criteria.

1. The severity of the stricture, judged on the results of oesophagoscopy and barium contrast studies, but essentially by its response to bouginage.
2. The severity and extent of pathological changes affecting the oesophageal wall, such as transmural fibrous scarring and the existence of a penetrating ulcer or perforation.

On the whole, conservative surgery was undertaken in the absence of a perforation or ulcer penetration and when the stricture could be dilated at the time of operation. In the majority of patients this decision could be made before surgery. In some cases, however, this was not possible.

Of the 87 patients, 49 were male and 38 female. Their ages ranged from 18 to 84 with an average of 62·2 years. The outstanding symptom of every patient was dysphagia: total dysphagia was present in 3 patients and the others could only manage a liquid and purée diet. The mean duration of dysphagia was 2·5 years. Every patient had undergone dilatation at least twice before admission for surgery. Fifteen of these patients had been treated elsewhere by repeated dilatations for a period of 1–10 years and were referred for surgery when the stricture was judged to be undilatable. Three patients had been practising daily self-bouginage for a period of 2–4 years. Six patients had had previous surgery for repair of a hiatal hernia.

Loss of weight averaging 6 kg was recorded in 30 patients. Anaemia was present in 10 patients and 6 others had acute bleeding, 3 of them with severe haematemesis at the time of admission.

Preoperative investigations included a barium swallow examination, oesophagoscopy and biopsy. The barium swallow demonstrated a stricture and hiatal hernia in every case.

The majority of patients had had previous barium swallow examinations, showing a hiatal hernia and stricture, from 1 to 18 years before admission.

Oesophagoscopy was carried out in every patient. The endoscopic characteristics and the level of the stricture from the upper alveolus were carefully recorded. Biopsies were taken from above, at the stricture and, when possible, from below it. Based on oesophagoscopic findings and bouginage a stricture was empirically classed as 'tight' when it was rigid and unyielding to the passage of bougies and 'moderately tight' when it was resistant and gripping but allowed the introduction of bougies of increasing diameter. A stricture was classed as 'not tight' when it allowed easy introduction of bougies of increasing diameter and offered no resistance to their passage. All patients in this series had a 'tight' or 'moderately tight' stricture (*Table I*).

The approximate overall length of the oesophagus and the level of the oesophageal hiatus for each patient were recorded using a technique similar to that described by d'Abreu et al.

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[illegible]		[illegible] with tight [illegible]cture	m[illegible]rately [illegible]ght [illegible]tricture	[illegible]
Dilata[illegible] strictu[illegible] [illegible]d Allison repair		14	20	[illegible]
Dilatation of stricture and intra-abdominal fundoplication	2a	10	21	31
Dilatation of stricture and intrathoracic fundoplication	2b	16	6	22

[illegible]ble II: LEVEL OF STRICTURE AND ITS [illegible]NSERVATIVE SURGERY IN REFLUX STRICTURE [illegible] THE OESOPHAGUS ASSOCIATED WITH [illegible]TAL HERNIA

[illegible]tion of [illegible]ture*	Total	Group 1	Group 2A	Group 2B
[illegible]	19	2	2	15
[illegible]	68	32	29	7

[illegible]igh defined as more than 4–5 cm above the hiatus.

Table III: LEVEL OF OESOPHAGOGASTRIC JUNCTION AS INDICATED BY THE PHRENO-OESOPHAGEAL MEMBRANE AT OPERATION AND ITS DISTRIBUTION IN 87 PATIENTS UNDERGOING CONSERVATIVE TREATMENT FOR REFLUX STRICTURE

Level of junction*	Total	Group 1	Group 2A	Group 2B
High	15	0	0	15
Low	72	34	31	7

* High defined as more than 4–5 cm above the hiatus.

Table IV: CONSERVATIVE SURGERY IN REFLUX STRICTURE OF THE OESOPHAGUS ASSOCIATED WITH HIATAL HERNIA

Group	No.	Deaths	No. requiring postop. dilatation	Resid. dysph.	Resid. htbn and reflux	Asymp.
1	34	2	4	1	2	26
2A	31	1	1	0	0	27
2B	22	0	0	0	0	22

Resid. dysph., residual dysphagia. Resid. htbn, residual heartburn. Asymp., asymptomatic.

(1971). From the endoscopic level of the stricture, the result of the barium swallow and the approximate length of the oesophagus, the location of the stricture in relation to the aortic arch and the diaphragmatic oesophageal hiatus were determined and recorded. In this way a comparable anatomical level of all the strictures, irrespective of the patient's size, was obtained. A stricture was classed as low when it was situated within 4–5 cm of the predicted oesophageal hiatus of the diaphragm and high when it was above this level. In this series, no stricture was situated above the aortic arch (*Table II*).

Operation

The operative approach consisted of a left thoracotomy in every case and the thoracic oesophagus was fully mobilized by [illegible]unt o[illegible] [illegible] Ac[illegible] abdomen was obtained [illegible]rcum[illegible] [illegible]dial [illegible] [illegible]erally placed diaphrag[illegible]. The [illegible] was e[illegible]ed first digitally through [illegible] location an[illegible] relationship with the hiatus [illegible]oesophagogastric juncti[illegible] were noted. The level of the [illegible]ageal membrane [illegible]ligament[illegible] indicating the [illegible]tric junction was also deter[illegible]ned and recorded [illegible] (*Table III*), using the preoperative criteria for [illegible] stricture as indicated previously. Transgastric [illegible] the stricture was then carried out by retrograde [illegible]gar bougies of increasing diameter, up to and [illegible]ng[illegible]m, introduced by one hand and guided by the [illegible]pl[illegible] over and around the oesophagus. Following the [illegible]tio[illegible] gastric incision was closed and one of two types [illegible] operation carried out. Thirty-four patients [illegible]p[illegible] [illegible]a[illegible] an Allison (1951) repair and 53 patients (group [illegible] Nissen (1956) fundoplication. In the latter the aim was [illegible] [illegible]bilize the oesophagus in order to bring the oesophagogastric junction, surrounded by the fundus of the stomach, below the diaphragm.

In 31 patients (group 2A) this was achieved, and this procedure is referred to as intra-abdominal fundoplication. In the remaining 22 patients (group 2B), in spite of full mobilization, this could not be achieved. Therefore, the fundoplication was placed permanently in the posterior mediastinum above the diaphragm. This is termed intrathoracic fundoplication. In both groups 2A and 2B the hiatus was reconstructed (*Table I*).

The allocation of patients to either group 1 or group 2 was governed by the anatomical disposition of the hiatus, the level of the stricture and the oesophagogastric junction found at operation, and whether there had been previous surgery. Consideration was given to the fact that a satisfactory repair in an Allison-type operation requires the integrity of the crural fibres, whereas a fundoplication requires a mobile fundus, particularly when the fundoplication is to be placed in the chest.

It is therefore clear that allocation of patients to groups 1, 2A and 2B was largely made at the time of operation.

Results

Table I presents the total number of patients in each group and the type of stricture. *Table II* shows the number of patients with high or low stricture, and *Table III* indicates the number of patients in each group with the oesophagogastric junction located high or low.

There were 3 hospital deaths in the entire series, a mortality of 3·4 per cent. One patient died 7 days postoperatively from pulmonary embolus and an 84-year-old man died 17 days postoperatively from a chest infection. These 2 patients were in group 1. The third patient, from group 2A, died from a myocardial infarction 24 h after surgery. The 84 surviving patients have been followed up for 6 months to 6 years (*Table IV*).

Group 1

There were 34 patients in this group, 14 with a tight stricture and 20 with a moderately tight stricture. Thirty-two patients survived the operation and 4 needed postoperative dilatation in the first year after surgery. One of these has residual dysphagia and awaits further surgery. Two other patients have no dysphagia but suffer from medically manageable heartburn and have evidence of reflux. The remaining 26 patients are asymptomatic. It is relevant to point out that each of the 4 patients who required postoperative dilatation had had a tight stricture before surgery. Also there were 2 high and 32 low strictures in this group. The 2 patients with high strictures are those with the residual symptoms of heartburn and reflux.

Group 2A
There were 31 patients in this group, 10 w[illegible] stricture and 21 with a moderately tight st[illegible] stricture was high in only 2 patients. Th[illegible] survived the operation: of these, 1 pat[illegible] dilatation on two occasions in the first 6 m[illegible] operation. Preoperatively, this patient [illegible] moderately tight stricture. Two patients [illegible] symptoms of fullness after meals. Twenty-seven patients have remained asymptomatic.

Group 2B
There were 22 patients in this group, 15 [illegible] a high and tight stricture and 7 with a low stricture, which was tight in only one. In the latter 7 patients, despite the low position of the stricture, the fundoplication could not be placed below the diaphragm. However, it must be pointed out that 4 of these patients had had previous surgery for repair of a hiatal hernia. There was no postoperative mortality in this group and all the patients have remained asymptomatic.

Discussion
The literature concerned with reflux stricture of the oesophagus and its surgical treatment is controversial. The principal cause of this seems to be that the structural changes in the oesophagus in response to gastric reflux vary in severity and type. Consequently, the experience and therapeutic approach of various workers have differed. This is borne out by the many 'rational approaches' to the treatment of the stricture that have emerged in the past 24 years. These range from simple bouginage to various oesophagoplastic procedures following excisional surgery.

Most surgeons have advocated resection of the stricture and reconstruction of the upper alimentary tract whenever the general condition of the patient permits the proposed surgical undertaking. However, the choice of operation and the substitute have been subject to the surgeon's preference. Oesophagogastric anastomosis has been employed by Sweet et al. (1954), Ellis et al. (1956), Collis (1957), Gavriliu (1965) and Franklin (1977).

The use of the jejunum was originally advocated by Roux (1907), and since then this approach has been favoured by a number of surgeons—Allison and Da Silva (1953), Brain (1953, 1967), Allison et al. (1957) and Gunning (1972). The use of the colon to replace the oesophagus has been practised since 1911 when it was introduced by Kelling. Its use in cases of benign oesophageal stricture, however, has been greatly popularized by Belsey (1953, 1965; Skinner and Belsey, 1967; Belsey et al., 1972).

A more conservative surgical method not requiring resection of the stricture was advocated by Collis (1957, 1961). He devised the operation of gastroplasty and suggested dilatation of the stricture to relieve the obstruction coupled with gastroplasty as an anti-reflux procedure in cases of oesophageal stricture, particularly in those with a high oesophagogastric junction (acquired short oesophagus). Pearson and co-workers (Pearson et al., 1971; Pearson and Henderson, 1973, 1976), used a combination of a Collis gastroplasty and a Belsey hiatus hernia repair as an anti-reflux operation coupled with preoperative or intraoperative dilatation to relieve the obstruction in patients with stricture and acquired short oesophagus. They reported excellent results in a selected group of patients with follow-up extended over a [illegible] years. [illegible] gastroplasty [illegible] [illegible] repair have not been [illegible] shown recently by Orringer [illegible] 197[illegible] [illegible]less, the procedure app[illegible] class of stricture, when [illegible] oesophagus is not desirable, and in the presence of an acquired short oesophagus with a high oesophagogastric junction.

Although it is generally agreed that bouginage alone is not a permanent solution to the problem of a stricture, dilatation combined with an anti-reflux operation has a logical chance of success. Hayward (1961a) and more recently Hill et al. (1970) and Herrington et al. (1975) have pursued this line of treatment with success by dilating the stricture and reducing the hernia.

There is, however, confusion about the criteria adopted for either preserving or resecting a fibrotic scarred gullet. The level of the stricture has always been of importance when selecting patients for conservative or excisional surgery. Normally the oesophagogastric junction is found approximately 2–[illegible] cm below the squamocolumnar epithelial junction which corresponds externally to the level of [illegible] peritoneal reflection and the attachment of [illegible] phreno-oesophageal membrane (ligament). This [illegible] well documented by Lerch (1950) and Hayward (1961b, c). In cases of hiatal hernia and gastro-oesophageal reflux it is generally agreed that the stricture develops at the squamocolumnar epithelial junction. Even when the tip of the stricture was high in the oesophagus, Allison believed that it extended down to within millimetres of the columnar epithelium of the stomach. Hayward (1961a) believed this not to be the case. Hill et al. (1970) also found that the level of the stricture did not correspond externally with the oesophagogastric junction. Based on this, these authors were able to mobilize the oesophagus and bring the oesophagogastric junction below the diaphragm irrespective of the level of the stricture.

Careful study of our cases makes us believe that, although the lowest part of the stricture does generally correspond with the original location of the squamocolumnar epithelial junction and the site of attachment of the phreno-oesophageal membrane, this is not always so. The latter may be situated considerably higher than the oesophageal hiatus of the diaphragm. This conclusion was reached by noting and recording the site of the stricture in relation to the oesophagogastric junction at operation by means of inserting a finger (or a Hegar bougie in the case of a high stricture) through the gastrotomy.

Study of *Tables II* and *III* shows that in 19 patients the position of the stricture was high but in only 15 of them was the location of the oesophagogastric junction correspondingly high. In 4 patients (4·5 per cent), therefore, the level of the stricture was higher than the external demarcation of the oesophagogastric junction. In these 4 cases (2 in group 1 and 2 in group 2) the junction could be placed beneath the diaphragm. In 7 patients from group 2B, although the junction and the stricture were within 5–6 cm of the hiatus, an intrathoracic fundoplication was necessary.

The practical conclusions are: first, that in 4·5 per cent of cases the level of the stricture is higher than the oesophagogastric junction. Secondly, more attention should be focused on the level of the junction [illegible] f the stricture [illegible] to be placed [illegible] the hernia is [illegible] the reduction of the [illegible] upon the level of the [illegible] oesophageal membrane [illegible] and [illegible] pathological changes [illegible] phagus [illegible] the perioesophageal structures. Our experience is therefore that in those who [illegible] that the junction can [illegible] down below the diaphragm in all cases. The placing of the fundoplication in the [illegible] antireflux measure has been satisfactory [illegible] p 2B patients, and overcomes the impossible [illegible] ing to reduce the oesophagogastric junction [illegible] diaphragm at all costs. The final decision [illegible] the fundoplication in the abdomen or the [illegible] n, however, be made at operation. Based on experience, we believe that neither the level of stricture nor the shortness of the oesophagus [illegible] tutes a criterion for radical surgery. The criterion should be whether the stricture can be satisfactorily dilated or not. An undilatable stricture should be excised.

It also appears that the preoperative assessment of the tightness of the stricture affects the postoperative results when an Allison-type operation is undertaken, as shown by the persistence of residual postoperative dysphagia and stricture in 4 out of the 14 patients with a tight stricture in group 1. In group 2, however, preoperative tightness of the stricture had no effect on the postoperative results.

Although our records show that 43 (33 per cent) of the 130 patients had radical surgery, 6 of these had resection because of oesophageal perforation in the course of dilatation of severely fibrotic strictures. In 16 other patients the resection was planned because of previous surgery, bleeding and extensive ulceration. Only in the remaining 21 patients (16 per cent of all cases) was the decision to undertake resection of the stricture made because the stricture could not be satisfactorily dilated at the time of operation. Taking into account the 6 perforation cases, a total of 27 patients (20 per cent) had resection of an undilatable stricture.

In 4 of our patients a stricture high above the oesophagogastric junction could be placed under the diaphragm at operation. Allison (1970) suggested that a high stricture well above the oesophagogastric junction is not a reflux stricture but results from oesophagitis at the high junction of the squamo-columnar epithelium. The controversy over the concept of columnar epithelium lining the oesophagus started in 1950 when Barrett drew attention to the condition. Allison and Johnstone (1953), termed this 'oesophagus lined with gastric mucous membrane' and believed it to be congenital in origin, a claim which has been rejected in many subsequent papers, notably those by Goldman and Beckman (1960), Adler (1963), Mossberg (1966) and, more recently, Hill et al. (1970). These authors believe that this condition is an acquired one resulting from oesophagogastric reflux. It therefore appears that whilst there is a general acceptance of the concept of a columnar-lined oesophagus, there is also a considerable body of opinion against its congenital origin.

Although there is controversy about the aetiology of columnar epithelium lining the oesophagus, there is complete agreem[illegible] rding the conservative approach to the treat[illegible] of the stricture resulting from it, as recommended by Allison (1970), Neaf and Savary (1972) and Davidson (1976).

Conclusions

The decision to offer a patient with a hiatal hernia and long-standing reflux stricture conservative or radical surgery should not depend on the level of the stricture but on its response or 'give' to dilatation and on whether the oesophagus can be preserved. This is best assessed at operation, as the preoperative impression of the severity of the stricture and its response to dilatation does not always correlate with the findings at operation. Conservative surgery consisting of dilatation of the stricture and an anti-reflux operation should be considered in every patient.

In our experience, the best way to achieve dilatation of a tight fibrotic and scarred stricture is at operation through a gastrotomy by retrograde and guided passage of bougies.

There are several surgical methods to prevent reflux following dilatation of a stricture. An Allison-type operation may be suitable when the oesophagogastric junction can be brought down below the diaphragm and when the anatomical disposition of the diaphragmatic crura is suitable for such a procedure. These two factors impose a serious limitation in patients with a stricture, and even in suitable cases the method has not been entirely satisfactory.

A Nissen-type fundoplication as an anti-reflux procedure may be used with advantage in all cases irrespective of the site of the oesophagogastric junction. If the junction cannot be reduced below the diaphragm, the fundoplication, that is, the lower oesophagus surrounded by the stomach and the fundus should be left in the chest above the diaphragm. The only limitation of this procedure is in cases when the fundus cannot be mobilized. The fundoplication has real advantages, however, in those patients with an irreducible oesophagogastric junction who otherwise would have to be submitted to more radical surgery.

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References

D'ABREU A. L., COLLIS J. L. and CLARKE D. B. (1971) *A Practice of Thoracic Surgery*, 3rd ed. London, Arnold, p. 475.

ADLER R. H. (1963) The lower oesophagus lined by columnar epithelium. *J. Thorac. Cardiovasc. Surg.* **45**, 13–34.

ALLISON P. R. (1951) Reflux oesophagitis, sliding hiatal hernia and the anatomy of repair. *Surg. Gynecol. Obstet.* **92**, 419–431.

ALLISON P. R. (1970) Peptic oesophagitis and oesophageal stricture. *Lancet* **2**, 199–202.

ALLISON P. R. and JOHNSTONE A. S. (1953) The oesophagus lined with gastric mucous membrane. *Thorax* **8**, 87–101.

ALLISON P. R. and DA SILVA L. T. (1953) The Roux loop. *Br. J. Surg.* **41**, 173–180.

ALLISON P. R., WOOLER G. H. and GUNNING A. J. (1957) Oesophago-jejuno-gastrostomy. *J. Thorac. Surg.* **33**, 738–748.

BARRETT N. R. (1950) Chronic peptic ulcer of the oesophagus and oesophagitis. *Br. J. Surg.* **38**, 175–182.

BELSEY R. (1953) Diaphragmatic hernia. *Trans. Med. Soc. Lond.* **68**, 18–29.

BELSEY R. (1965) Reconstruction of the oesophagus with left colon. *J. Thorac. Cardiovasc. Surg.* **49**, 33–55.

BELSEY R., ABBEY SMITH R. and SMITH R. E. (1972) The long term clinical state after resection with colon replacement in adults. *Surgery of the Oesophagus* (The Coventry Conference). London, Butterworths, pp. 41–45.

BRAIN R. H. F. (1953) Steatorrhoea in oesophago-gastric surgical practice. *Proc. R. Soc. Med.* **46**, 438–444.

BRAIN R. H. F. (1967) The place for jejunal transplantation in the treatment of simple strictures of the oesophagus. *Ann. R. Coll. Surg. Engl.* **40**, 100–118.

COLLIS J. (1957) An operation for hiatus hernia with short oesophagus. *Thorax* **12**, 181–188.

COLLIS J. L. (1961) Gastroplasty. *Thorax* **16**, 197–206.

DAVIDSON J. S. (1976) High peptic stricture of the oesophagus. *Thorax* **31**, 1–14.

ELLIS F. H., ANDERSEN H. A. and CLAGETT O. T. (1956) Surgical management of the complications of reflux oesophagitis. *Arch. Surg.* **73**, 578–589.

FRANKLIN R. H. (1977) The advancing frontiers of oesophageal surgery. *Ann. R. Coll. Surg. Engl.* **59**, 284–287.

GAVRILIU D. (1965) État actuel du procédé de reconstruction de l'oesophage par tube gastrique—1138 malades opérés. *Ann. Chir.* **19**, 219–224.

GOLDMAN M. C. and BECKMAN R. C. (1960) Barrett syndrome—case report with discussion about concept of pathogenesis. *Gastroenterology* **39**, 104–110.

GUNNING A. J., ABBEY SMITH R. and SMITH R. E. (1972) The long-term clinical state after resection with jejunal replacement. *Surgery of the Oesophagus* (The Coventry Conference). London, Butterworths, pp. 29–33.

HAYWARD J. (1961a) The treatment of fibrous stricture of the oesophagus associated with hiatal hernia. *Thorax* **16**, 45–55.

HAYWARD J. (1961b) The lower end of the oesophagus. *Thorax* **16**, 36–41.

HAYWARD J. (1961c) The phreno-oesophageal ligament in hiatal hernia repair. *Thorax* **16**, 41–45.

HERRINGTON L. L., WRIGHT R. S., EDWARDS W. H. et al. (1975) Conservative surgical treatment of reflux oesophagitis and oesophageal stricture. *Ann. Surg.* **181**, 552–566.

HILL L. D., GELFAND M., BAUERMEISTER D. (1970) Simplified management of reflux oesophagitis with stricture. *Ann. Surg.* **172**, 638–651.

KELLING [illegible] *Ze*[illegible]

[illegible] (1965) The [illegible] drome): an [illegible] –676.

[illegible] T. and SAVAR[illegible] peptic oesophagitis [illegible] oesophagus. *Ann.* [illegible] 13, 543–[illegible]

NISSEN R. (1956) Eine [illegible] Operation zur Be[illegible] Reflux Oesophagitis [illegible] *Schweiz. Med. W*[illegible] 590–592.

ORRINGER M. B. and S[illegible] (1977) Complications of the combined [illegible]-Belsey operation. [illegible] *Cardiovasc. Surg.* [illegible]4, [illegible] 735.

PEARSON F. G. and HENDERSON R. D. (1973) Exper[illegible] clinical studies of gastroplasty in the man[illegible] acquired short oesophagus. *Surg. Gynecol. O*[illegible] 737–744.

PEARSON F. G. and HENDERSON R. D. (1976) Long-term [illegible] of peptic strictures managed by dilatation, modifi[illegible] gastroplasty and Belsey hiatus hernia repair. *S*[illegible] 396–404.

PEARSON F. G., LANGER B. and HENDERSON M. B. (1971) G[illegible] plasty and Belsey hiatus hernia repair: an opera[illegible] the management of peptic stricture with acqui[illegible] oesophagus. *J. Thorac. Cardiovasc. Surg.* **61**, 50–6[illegible].

ROUX C. (1907) L'Œsophago-jéjuno-gastrostomie. Nou[illegible] opération pour rétrécissement infranchissable [illegible] l'œsophage. *Semin. Med.* **27**, 37–40.

SKINNER D. B. and BELSEY R. (1967) Surgical management of oesophageal reflux and hiatus hernia. *J. Thorac. Cardiovasc. Surg.* **53**, 33–54.

SWEET R. H., ROBBINS L. L., GEPHART T. et al. (1954) Surgical treatment of peptic ulceration and stricture of the lower oesophagus. *Ann. Surg.* **139**, 258–268.

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geal perforations with ce t an scopic method

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copic treatment of chr oesophageal per- (more than 18–24 h old) the application of ydroxide 20 per cent to the edges of the rfora- described. The importance of pleural and medi- toilet and the accurate siting of drainage tubes ull expansion of the lung together with measures diminishing oral, gastric and biliary secretions from perforation, are stressed.

Five patients who have been treated by this conservative method are presented and the method compared with the more radical surgery advocated by the majority of other surgeons.

PERFORATIONS of the oesophagus may occur in the cervical oesophagus or the intrathoracic oesophagus. The causes are instrumental, traumatic, or the result of spontaneous or strain-induced ruptures or intrinsic oesophageal disease.

Cervical perforations

Perforations of the cervical oesophagus resulting in mild crepitus, extravasation of fluid but with no thoracic involvement are treated by oral and systemic antibiotics, by stopping oral feeds and by providing intravenous alimentation. Extensive leaks, causing widespread crepitus and dissection of extravasated material down the anterior or posterior mediastinum with a retro-oesophageal abscess, require operative drainage plus antibiotics and the feeding regimen outlined above. With proper and prompt treatment, perforations of the cervical oesophagus have a low mortality.

Thoracic perforations

Ever since Barrett's report (1947) of the successful repair of a spontaneous rupture of the oesophagus, the treatment of thoracic oesophageal perforations has been associated with a high mortality and morbidity. It is generally agreed that if a thoracic perforation is diagnosed within 18 h, the best results are obtained by primary suture of the perforation; the mortality rate then varies between 10 and 15 per cent. Surgical treatment after 18 h increases the mortality to 50 per cent. Any method, therefore, which can reduce this figure should be tried, and it is hoped that the method described below will go some way to achieving this.

Unfortunately, most thoracic oesophageal perforations are diagnosed after 18–24 h. By this time a severe and often fulminating chemical and infective mediastinitis and pleurisy are well established. These are caused by the aspiration of gastric, biliary and oral (often aggravated by dental sepsis) secretions through the perforation, by the intrathoracic subatmospheric pressure. The oesophagus is oedematous and friable and attempts at closure by suturing the defect are unsuccessful. The difficulty experienced in treating this condition is shown by the variety of surgical procedures reported.

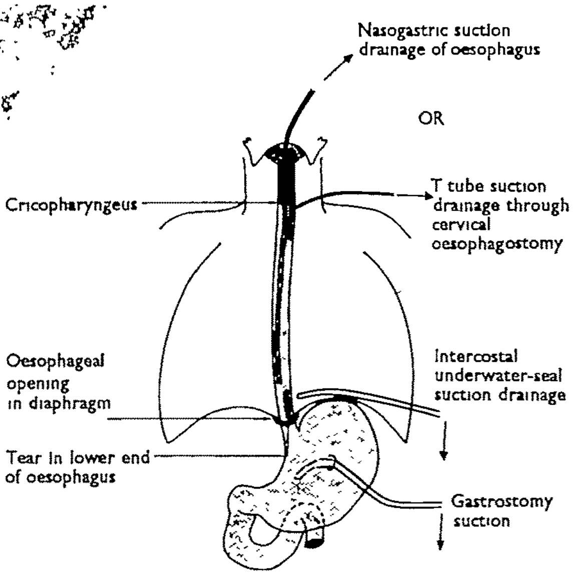
Nasogastric suction drainage of oesophagus
OR
T tube suction drainage through cervical oesophagostomy
Cricopharyngeus
Oesophageal opening in diaphragm
Intercostal underwater-seal suction drainage
Tear in lower end of oesophagus
Gastrostomy suction

Fig. 1. Diagram showing siting of the drainage tubes.

For example, Thal (1968) uses a patch of the fundus of the stomach which is applied to the perforation. Urschel et al. (1974) apply an umbilical tape around the lower end of the oesophagus to occlude it and divert oral secretions by a cervical oesophagostomy in addition to suturing the perforation. Grillo and Wilkins (1975) use a pedicled pleural flap which is wrapped around the oesophagus. Pericardium may also be used in this way. Triggiani and Belsey (1977) prefer total resection of the oesophagus leaving the patient with a cervical oesophagostomy to divert swallowed saliva and a feeding gastrostomy, the cardia having been closed by sutures. A staged reconstruction at a later date with the left colon restores intestinal continuity.

Patients and methods

Since 1975 the Thoracic Surgical Unit at the Churchill Hospital, Oxford, has used a more conservative approach utilizing the following principles.

Treatment of shock: If the patient is shocked, resuscitative measures such as fluid replacement, antibiotics, digitalis, relief of pain and intercostal tube drainage are instituted until the patient is fit for operation.

Diagnosis: The diagnosis can be made from symptoms, signs and a plain chest radiograph showing mediastinal emphysema and/or a hydropneumothorax in the right or left pleural cavity. The diagnosis and site of a suspected perforation should, if possible, be confirmed by a Gastrografin contrast swallow. However, a negative oesophagogram does not rule out a tear (Defore et al., 1977).

Treatment: The following steps are then taken to establish drainage of the mediastinum and pleura and full expansion of the lung (*Fig.* 1). Mediastinal, pleural toilet and intercostal

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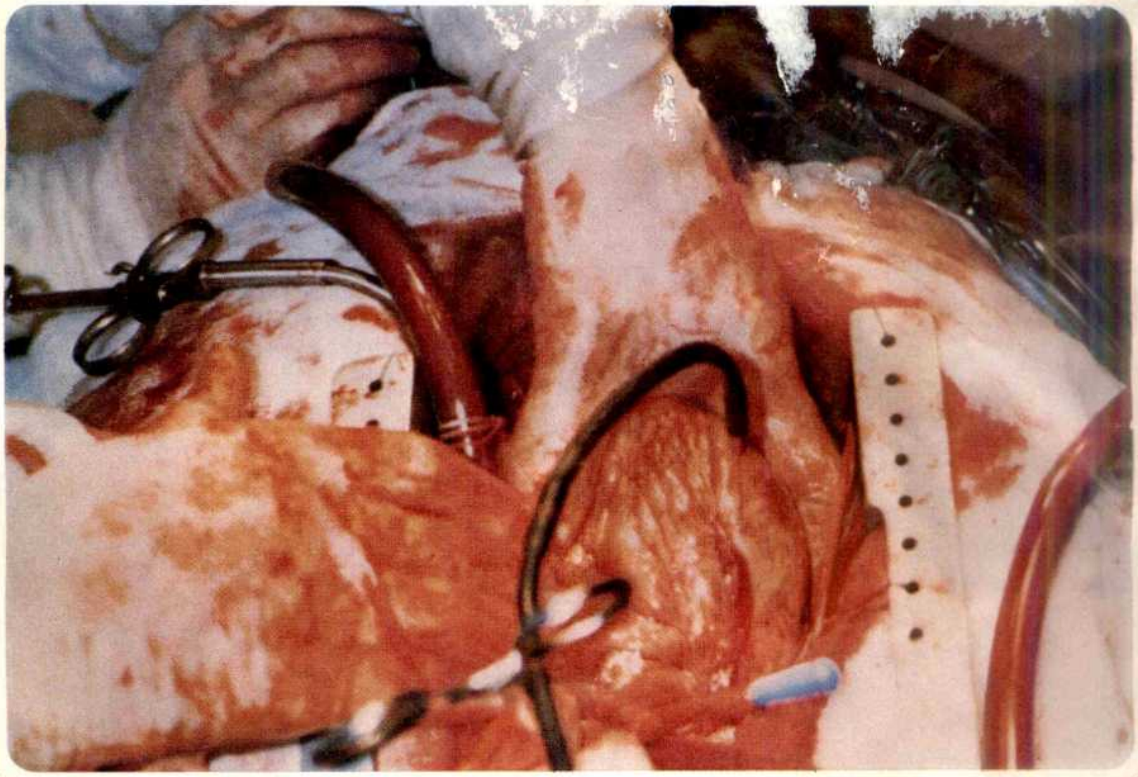
* Department of Thoracic Surgery, Churchill Hospital, Oxford.

Magnapen

ampicillin/[illegible]



Reliable antibiotic cover for the at-risk patient.

In cardiothoracic surgery, infection poses a special threat. It is essential to reduce the risk to an absolute minimum with prophylactic antibiotic cover[1].

Magnapen is of proven value in prophylaxis. In a recent study of 221 patients undergoing thoracotomy for lung resection[2] of whom 181 received Magnapen cover, the author concluded that "There was a significantly reduced incidence of pneumonectomy space infection, post-operative pneumonia and wound infection after pneumonectomy and lobectomy in those patients receiving prophylactic antibiotics compared with those not receiving prophylactic antibiotics."

Magnapen combines the broad spectrum of ampicillin with the anti-staphylococcal activity of flucloxacillin. It can thus be relied on to eliminate virtually all strains of staphylococci[3,4], Strep. viridans[5] and other likely wound pathogens.

1. Brit. med. J. (1978), **1**, 1603.
2. Thorax (1978), 33, **1**, 130.
3. Brit. med. J. (1978), **2**, 536.
4. Brit. med. J. (1970), **4**, 455.
5. Zbl. Bakt. Hyg., I. Abt. Orig. A. (1976), **236**, 235.

Prescribing Information

Magnapen Capsules: Black and turquoise capsules overprinted "Magnapen" containing 250mg ampicillin as Ampicillin Trihydrate B.P. with 250mg flucloxacillin as flucloxacillin sodium.
Magnapen Syrup: Bottles containing powder for the preparation of 100ml suspension. When reconstituted each 5ml contains 125mg ampicillin as Ampicillin Trihydrate B.P. with 125mg flucloxacillin as flucloxacillin sodium.
Magnapen Vials: Each vial contains 250mg ampicillin as Ampicillin Sodium B.P. with 250mg flucloxacillin as flucloxacillin sodium.
Uses: Severe infections. Post-operative chest and wound infections. Prophylaxis in major surgery.

Dosage: Adult: 1 capsule or 10ml syrup, or 1 vial qid. Children: 2-10 years: ½ adult dose. Under 2 years: ¼ adult dose. Ampiclox Neonatal (regd.) is recommended for the treatment of infections in neonates and premature babies. PL0038/5001, 5009.
Contra-indications: Penicillin hypersensitivity, ocular administration.
Side-effects: As with other penicillins. An erythematous rash may occasionally occur, as with ampicillin. The incidence of this rash is particularly high in patients with infectious mononucleosis. If a rash is reported, it is advisable to discontinue treatment.
Pharmaceutical Precautions: Magnapen solutions for injection should be used immediately. Consult product literature before using with intravenous fluids.

Basic N.H.S. Prices: (correct at time of printing Feb 79).
Capsules: 500mg, £18.06 (100 capsule pack).
Syrup: 250 mg per 5 ml, £3.18 (100ml).
Vials: 500mg, £7.45 (10 vials).

Magnapen is available to hospitals on regional contract dependent upon estimated usage.

Further information on Magnapen is available on request to the company.

Magnapen, BRL and the Company logo are registered trade marks.

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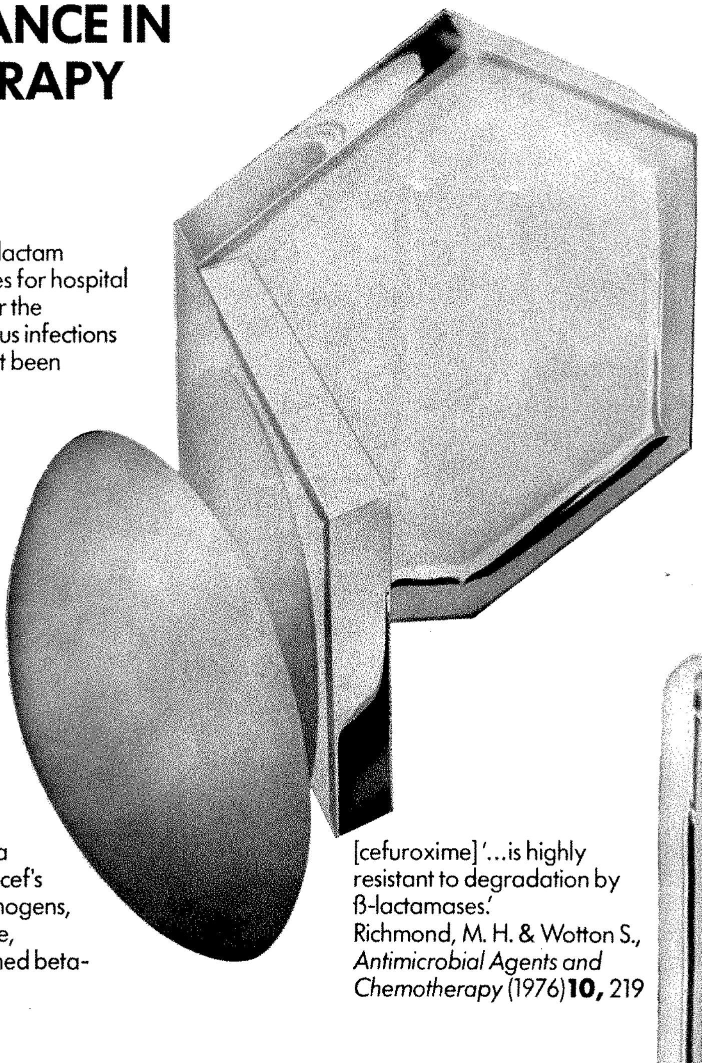
BRL 2024



INJECTABLE

ZINACEF

cefuroxime sodium

A MAJOR ADVANCE IN ANTIBIOTIC THERAPY

Zinacef is a new, broad spectrum, beta-lactam antibiotic offering important advantages for hospital practice. It is particularly appropriate for the treatment of serious, or potentially serious infections where the causative organisms have not been identified or may be mixed.

Greatly enhanced stability to beta-lactamases

The value of commonly used beta-lactam antibiotics is being constantly eroded by the growth of resistant populations of bacteria.
Zinacef has a unique chemical structure with in-built protection against beta-lactamases which effectively places it in a new class of antibiotics.

A broader spectrum than most antibiotics

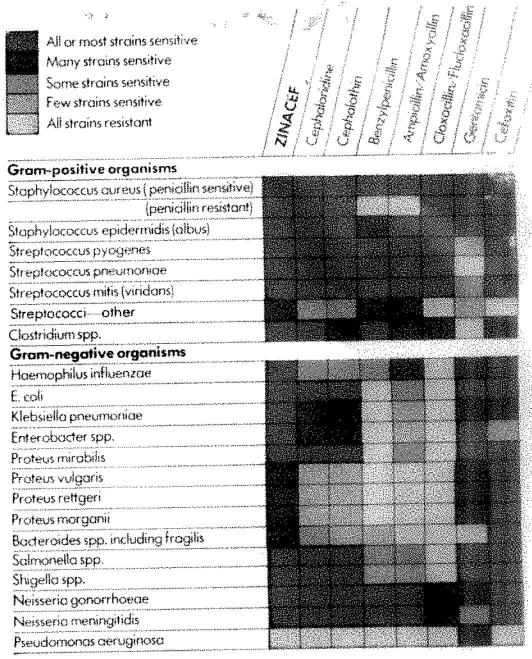
The ability to resist destruction results in a greatly extended clinical spectrum. Zinacef's bactericidal effect extends to many pathogens, both Gram-positive and Gram-negative, resistant or partially resistant to established beta-lactam antibiotics.

[cefuroxime] '...is highly resistant to degradation by ß-lactamases.'
Richmond, M. H. & Wotton S., *Antimicrobial Agents and Chemotherapy* (1976) **10,** 219

With important therapeutic properties

- Zinacef has high bactericidal activity.
- Adequate serum levels are rapidly achieved and are well maintained.
- Zinacef is widely distributed with adequate levels in sputum, bile, bone and cerebrospinal fluid.
- Zinacef is not metabolised, but excreted, active and unchanged, in the urine.
- Zinacef has minimal toxicity, giving a wide margin of safety.
- Clinical trials have shown excellent renal tolerance.
- Zinacef can safely be used in neonates.
- Patient tolerance is excellent both intramuscularly and intravenously.
- Zinacef is compatible with commonly-used intravenous infusion fluids.
- There are no known clinically relevant adverse drug interactions.
- Zinacef can be used with other antibiotics to increase the antibacterial cover.

'…this wide antibacterial cover [illegible] [Zinacef] a useful antibiotic for the treatment of infections requiring prompt parenteral therapy before the causative pathogen has been identified.'
British Medical Journal (1978) **1**, 12[illegible]



All or most strains sensitive
Many strains sensitive
Some strains sensitive
Few strains sensitive
All strains resistant

ZINACEF
Cephaloridine
Cephalothin
Benzylpenicillin
Ampicillin/Amoxycillin
Cloxacillin/Flucloxacillin
Gentamicin
Cefoxitin

Gram-positive organisms
Staphylococcus aureus (penicillin sensitive)
(penicillin resistant)
Staphylococcus epidermidis (albus)
Streptococcus pyogenes
Streptococcus pneumoniae
Streptococcus mitis (viridans)
Streptococci—other
Clostridium spp.

Gram-negative organisms
Haemophilus influenzae
E. coli
Klebsiella pneumoniae
Enterobacter spp.
Proteus mirabilis
Proteus vulgaris
Proteus rettgeri
Proteus morganii
Bacteroides spp. including fragilis
Salmonella spp.
Shigella spp.
Neisseria gonorrhoeae
Neisseria meningitidis
Pseudomonas aeruginosa

ZINACEF

Prescribing information

Presentation
Vials of 250mg, 750mg and 1·5 gram and infusion pack of 1·5 gram. All containing cefuroxime as cefuroxime sodium.

Indications
Serious bacterial infection, especially where the organisms have not yet been identified.
Conditions include:
Chest infections
Septicaemia
Soft tissue infections
Obstetric and gynaecological infections
Bone and joint infections
Urinary tract infections
Ear, nose and throat infections
Meningitis
Gonorrhoea

Dosage
Adults: Generally 750mg t.d.s. i.m. or i.v. Severe infections 1·5 gram t.d.s. i.v. Frequency of injections can be increased to six-hourly if necessary.
Infants and children: 30 to 100mg/kg/day in three or four divided doses. 60mg/kg/day will be appropriate for most infections.
Neonates: 30 to 100mg/kg/day in two or three divided doses.
Gonorrhoea: Single dose of 1·5 gram (2 x 750mg i.m. into different sites).

Contra-indications
Hypersensitivity to cephalosporins.

Precautions
Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins.
As with all drugs, Zinacef should be administered with caution during the early months of pregnancy.
Zinacef does not interfere with enzyme-based tests for glycosuria.
Cephalosporins interfere with tests for glycosuria which use copper reduction or ferricyanide methods and with the alkaline picrate assay for creatinine.
As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms.
Zinacef should not be mixed in the syringe with aminoglycoside antibiotics.
Reduce dosage when renal function is markedly impaired.
Cephalosporins at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as frusemide, as these combinations are suspected of adversely affecting renal function. Clinical experience with Zinacef has shown that this is not likely to be a problem at the recommended dose levels.

Side effects
Adverse reactions are rare and generally mild and transient, e.g., rashes, gastro-intestinal disturbance, candida intertrigo, decreased haemoglobin concentration, eosinophilia, a positive Coombs' test, transient rises in serum liver enzymes and transient pain (after i.m. injection).

Storage
The powder in the infusion pack and vials should be stored below 25°C and protected from light.

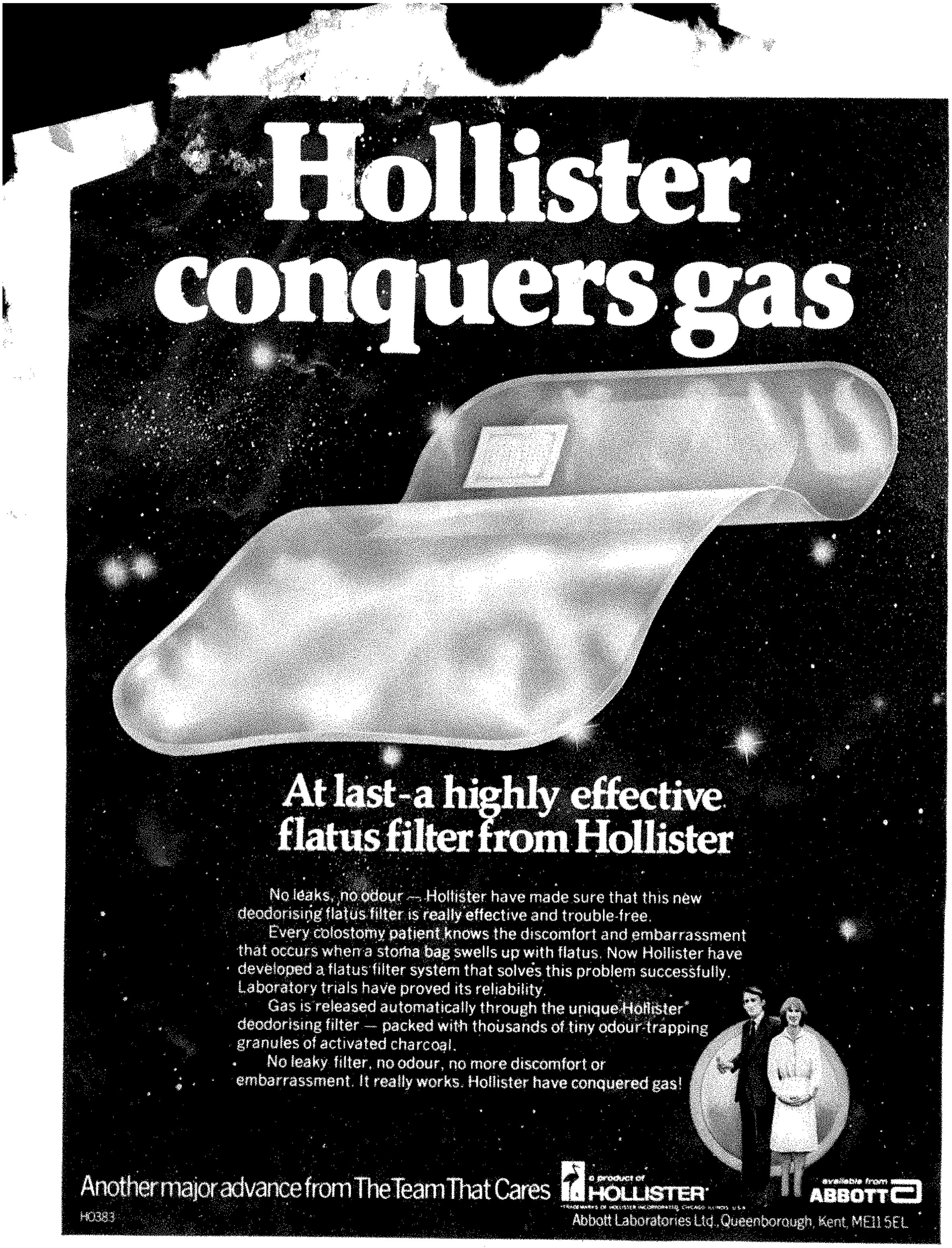
Product Licence number
4/0263

Price to Hospital (exclusive of VAT)

	£
5 x 250mg	0·70 per vial
5 x 750mg	2·10 per vial
1·5 gram	4·20

Glaxo

Full prescribing information on Zinacef (trade mark) is available from:
Glaxo Laboratories Limited
Greenford, Middlesex UB6 0HE



Hollister conquers gas

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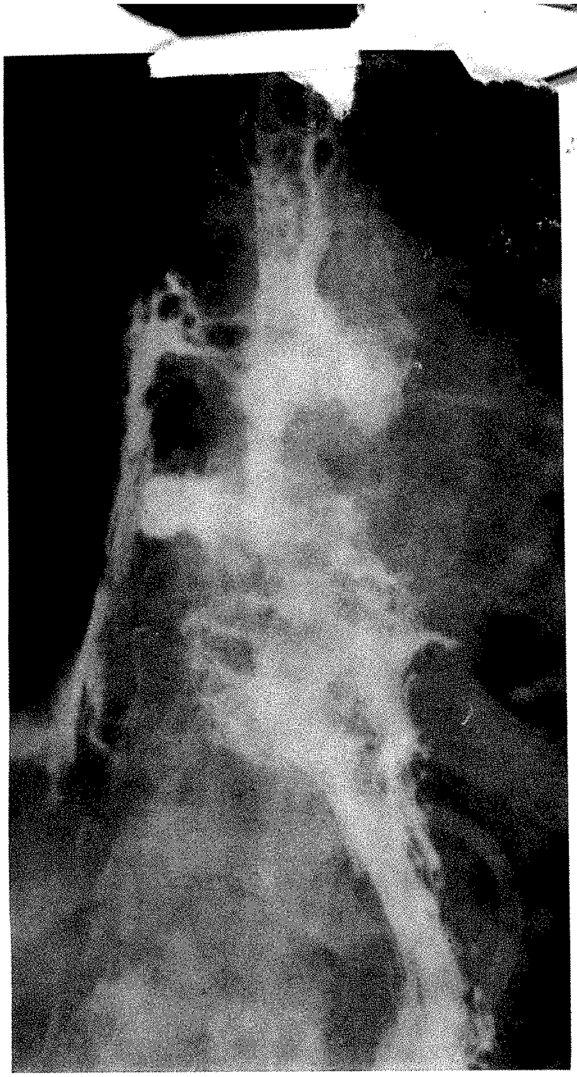

Fig. 2. (*Case* 1.) Radiograph showing leak from oesophago-gastroplasty.

tube drainage are performed through a small thoracotomy, on whichever side shows a hydropneumothorax, or into which pleural cavity there is extravasation of Gastrografin. The drainage tubes are placed next to the perforation to establish an oesophagocutaneous fistula and to drain the pleural cavity and mediastinum. Continuous suction is applied to the tubes through an underwater seal to ensure full expansion of the lung which will adhere to the parietal pleura around the tube and eliminate any space where air or fluid may persist to form an empyema (Froggatt and Gunning, 1966). This is the most important part of the treatment.

A gastrostomy is performed and the tube is connected to a Robert's suction pump to remove gastric secretions and/or any refluxed bile. This is especially important in low oesophageal tears where incompetence of the lower oesophageal sphincter causes persistent gastro-oesophageal reflux which is increased by the negative intrathoracic pressure.

The oesophagus is kept empty by suction applied to an indwelling naso-oesophageal tube or a T tube placed in a cervical oesophagostomy.

All patients are given tetracycline syrup and a fungicide by mouth so that a bolus of antibiotic reaches the most contaminated area. Wide spectrum systemic antibiotics are given during the acute stage of mediastinitis.

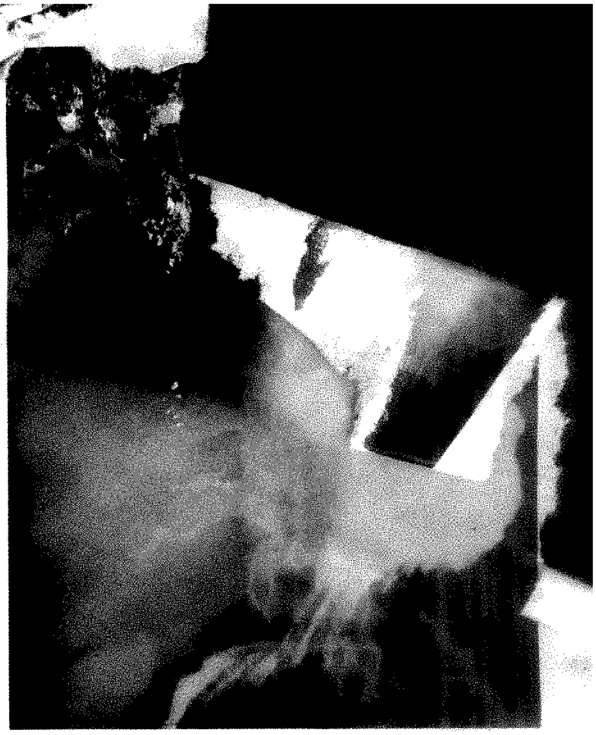

Fig. 3. (*Case* 1.) Gastrografin swallow showing healed perforation.

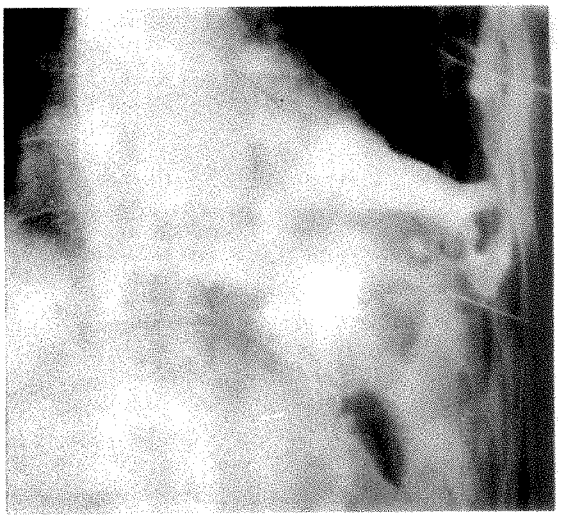

Fig. 4. (*Case* 2.) Gastrografin swallow showing leak from lower end of oesophagus.

Oral intake is stopped. These patients lose large amounts of protein and electrolyte-rich fluid which must be replaced in addition to the normal daily requirements of water, electrolytes, nutrients, vitamins and trace elements. The amounts to be replaced are achieved by keeping an accurate intake and output fluid chart which is reviewed every 24 h. Fluid and nutritional requirements are supplied by intravenous alimentation, the intravenous cannula being inserted into a subclavian vein by the infra- or supraclavicular route and changed every 7 days. Alternatively, jejunostomy feeding may be given through a tube introduced into the stomach and threaded

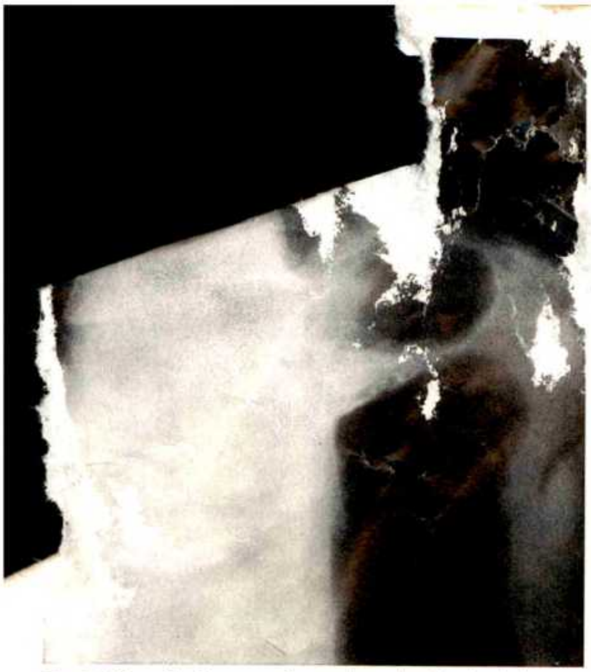

Fig. 5. (*Case* 2.) Gastrografin swallow showing healed perforation.

[illegible] into the jej [illegible] as the gastrostomy is performed.

Local treatment of the perforation by cauterization with 20 per cent sodium hydroxide is commenced at this time.

The patient is anaesthetized and the perforation visualized through a rigid oesophagoscope. Cotton wool pledgets are soaked in 20 per cent sodium hydroxide and then applied to the edges of the perforation with an applicator or forceps. Three or four applications are made of approximately 1 min duration. The sodium hydroxide is then neutralized with a 30 per cent solution of acetic acid. This procedure is repeated at weekly intervals until the perforation closes. Progress of closure is monitored by Gastrografin swallows (Froggatt and Gunning, 1966).

This method is illustrated in the following 5 case reports. There were no deaths. All the patients reported are now able to eat and drink without difficulty.

Case reports

Case 1: Mrs M. F., aged 49, underwent oesophagoplasty and a Nissen fundoplication (Nissen, 1956) for a congenital oesophageal stricture. A breakdown of the oesophageal suture line (*Fig.* 2) was diagnosed on the fifth postoperative day. The general measures described above were instituted and she was treated on the fourteenth postoperative day and twice thereafter with alkaline cauterization. The perforation healed (*Fig.* 3) and she was discharged 3 weeks later.

Case 2: Mr D. S., aged 43, presented with a 9-month history of dysphagia caused by achalasia of the cardia. A Heller's oesophagomyotomy was performed. Two days later a collection of fluid in the left pleural cavity and a small pneumothorax were shown to be present (*Fig.* 4). Three alkaline

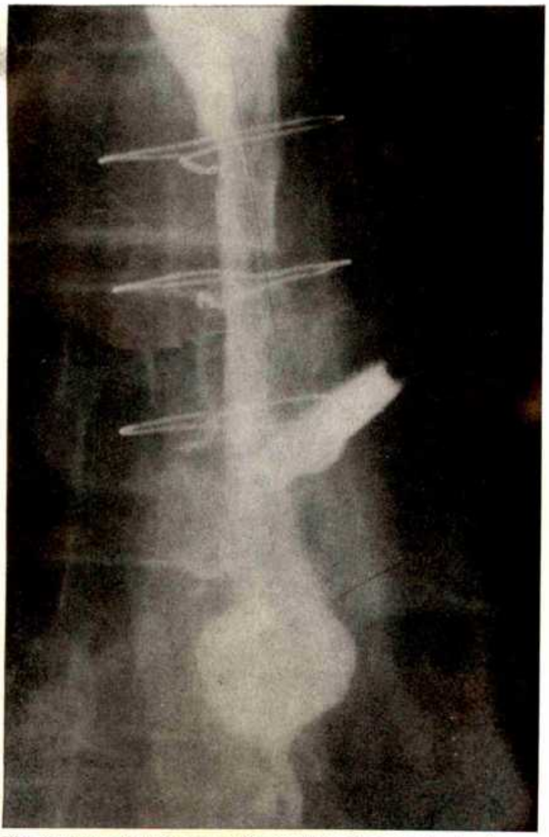

Fig. 6. (*Case* 3.) Gastrografin swallow showing leak of contrast medium from oesophageal perforations. Note previous aortic valve replacement.

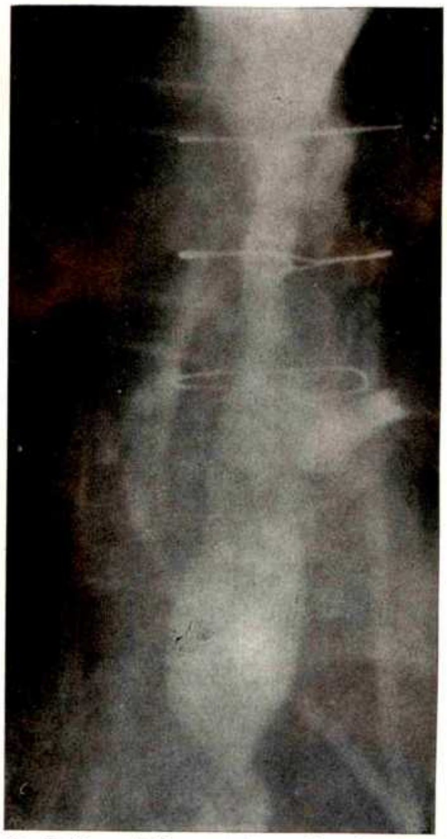

Fig. 7. (*Case* 3.) Gastrografin swallow showing closure of the perforation.

asymptomatic

Case 3: Mr D. M.
of the oesophagus.
and one posterior in gus
the anterior and poste ars were sutured. A
placed around the lower end of the oesophagus and rvical
oesophagus drained by a T tube cervical oesophagostomy. This was done because at surgery it was felt that oesophageal replacement would be necessary. (*Fig*. 6 shows a Gastrografin swallow performed a week later and shows a persistent leak posteriorly.) This posterior tear required two alkaline cauterizations before closure. The ligature around the lower oesophagus was removed with some difficulty and the oesophagostomy closed spontaneously after removal of the T tube. He suffered no dysphagia and was able to eat normally (*Fig*. 7).

Case 4: Mrs E. D., aged 55, was another patient with spontaneous rupture of the oesophagus which occurred during an epileptic fit. She was moribund and was artificially ventilated for 2 weeks and was at first thought to have only a pneumothorax. A 4-cm oesophageal perforation at 30 cm was later diagnosed. She had weekly cauterization over a period of 2 months with gradual closure of the perforation. Her perforation healed, but she required decortication of an empyema cavity which developed due to inadequate drainage of the pleural cavity in the early stages and which we believe prolonged the closure of the perforation.

Case 5: Mr S. M., aged 71, developed a leak from the suture line after excision of a pharyngeal pouch which failed to close spontaneously. One alkaline cauterization resulted in closure of the perforation and he was able to swallow normally.

Discussion

A previous report from this unit (Froggatt and Gunning, 1966) advocated a relatively conservative approach for the treatment of chronic oesophageal perforations. However, in other centres more aggressive procedures have been adopted as the mortality associated with this 'drain and hope' method is said to be between 15 per cent and 50 per cent (Loop and Groves, 1970; Triggiani and Belsey, 1977).

This figure is too high (Leading Article, 1977) and can be drastically reduced by meticulous toilet and drainage of the mediastinum and pleural cavity in the first instance, followed by cauterization of the perforation with the local applications of sodium hydroxide to close the defect. This simple, but ingenious, technique was described by McCluskie (1975) and there is only one other report of its use (Agosti et al., 1978). Caustic irritation of the oesophageal mucosa

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e are indebted to Miss Sylvia
artwork and to M Julie Cook and
typing the manuscript.

References

AGOSTI J., NOJEK C. and FIGUERA D. (1978) Th
acquired chronic oesophageal fistula by
cauterization. *Chest* **73**, 100–102.

BARRETT N. R. (1947) Report of a case of spontaneous pe
tion of the oesophagus successfully treated by ope
Br. J. Surg. **35**, 216–218.

DEFORE W. W. JUN., MATTOX K. L., HANSEN H. A. et al. (
Surgical management of penetrating injuries of
esophagus. *Am. J. Surg*. **134**, 734–738.

FROGGATT D. L. and GUNNING A. J. (1966) Treatment of oesophageal perforation. *Thorax* **21**, 524–528.

GRILLO H. C. and WILKINS E. W. (1975) Esophageal repair following late diagnosis of intrathoracic perforation. *Ann. Thorac. Surg*. **20**, 387–399.

LEADING ARTICLE (1977) Management of oesophageal perforation. *Br. Med. J*. **2**, 540.

LOOP F. D. and GROVES L. K. (1970) Esophageal perforations. *Ann. Thorac. Surg*. **10**, 571–587.

MCCLUSKIE R. A. (1975) Endoscopic treatment of late oesophageal fistulae. Paper read before the Society of Thoracic and Cardiovascular Surgeons of Great Britain and Ireland, Glasgow, September 1975.

NISSEN R. (1956) Eine einfache Operation zur Beeinflussung des Reflux Oesophagitis. *Schweiz. Med. Wochenschr*. **86**, 590–593.

TRIGGIANI E. and BELSEY R. (1977) Oesophageal trauma: incidence, diagnosis and management. *Thorax* **32**, 241–249.

THAL A. P. (1968) A unified approach to surgical problems of the oesophagogastric junction. *Ann. Surg*. **168**, 542–550.

URSCHEL H. C., RAZZUK M. A., WOOD R. E. et al. (1974) Improved management of esophageal perforation: exclusion and diversion in continuity. *Ann. Surg*. **179**, 587–591.

Paper accepted 10 November 1978.

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aat such a procedure may impair the
blooa the lesser curve, and they provide an anatomical explanation of the occasional occurrence of necrosis of the lesser curve following proximal gastric vagotomy.

In recent years the use of the mobilized stomach to replace the oesophagus in part, as in operations for carcinoma of the stomach (McKeown, 1976), or in its entirety, as in the treatment of post-cricoid carcinoma (Le Quesne and Ranger, 1966), has received increasing attention. In these operations all the vascular connections of the stomach are divided except for the right gastroepiploic and right gastric vessels; these are quite small, so that, in effect, the fundus of the stomach is dependent upon an anastomotic circulation stemming from the right gastroepiploic artery. According to McKeown (1976), the extragastric portions of the left gastric artery, lying along the lesser curve of the stomach, form an essential part of this anastomotic circulation, and hence must be preserved. However, Akiyama does not believe that these vessels play an important part in maintaining the viability of the fundus, and describes operations in which they are excised (Akiyama et al., 1976).

To clarify this problem a study has been carried out to determine whether, following the ligation of all the arteries to the stomach save only the right gastroepiploic, the viability of the fundus can be maintained solely by an intramural anastomotic circulation, or whether the extragastric arcade on the lesser curve is an essential component of the anastomotic supply to the fundus. In the event, the study also suggested an anatomical basis for the occurrence of lesser curve necrosis following the operation of proximal gastric vagotomy (highly selective vagotomy).

Materials and methods

Studies were carried out on 22 stomachs obtained at autopsy, 12 from men and 10 from women whose ages ranged from 19 to 90 years (average 67·5 years). Details concerning these subjects are set out in *Table I*. Specimens were not removed from subjects having gastrointestinal disease. Two injection techniques were used: the first used Chromopaque (Damancy and Co. Ltd) to obtain a two-dimensional picture of the region supplied by the cannulated vessel, and the second method employed a resin cast technique to define the exact pathway of the perfused vessels.

AUTOPSY SUBJECTS
MACHS WERE REMOVED

			Cause of death	Blood pressure (mmHg)
		31	Cerebral infarction	170/90
		83	Bronchopneumonia	150/80
3	F	49	Pulmonary embolus	120/70
4	F	63	Carcinomatosis breast	140/90
5	M	75	Carcinoma bronchus	175/80
6	M	70	Cerebral haemorrhage	140/90
7	F	58	Cardiac failure	120/80
8	M	58	Drowning (asphyxia)	?
9	F	90	Coronary thrombosis	160/90
10	M	69	Pulmonary embolus	140/70
11	M	19	Multiple injuries	?
12	M	35	Inhaled vomitus	?
13	F	68	Coronary thrombosis	140/80
14	F	77	Bronchopneumonia	160/90
15	M	64	Carcinoma bronchus	140/80
16	M	44	Cerebral laceration	130/70
17	F	68	Bronchopneumonia; CVA	120/80
18	M	67	Pulmonary embolus	120/85
19	F	75	Bronchopneumonia	140/90
20	F	70	Hypertension; cerebral haemorrhage	190/105
21	M	39	Teratoma testis	110/70
22	M	64	Coronary thrombosis	140/80

Eight patients died from consequences of arteriosclerosis; 9 further patients had evidence of significant atheroma, of whom 2 had atheroma affecting the gastric vessels.

Chromopaque technique (18 stomachs)
In the course of a routine autopsy, each stomach was excised with its blood vessels intact, the short gastric vessels being divided close to the spleen. The oesophagus was divided 5 cm above the oesophagogastric junction and left open, whilst the duodenum was transected 2·5 cm beyond the pylorus and closed after washing out any stomach contents. The stomach was placed on a dissecting surface and the artery to be injected was identified throughout its course. All other vessels to the stomach were then dissected out, ligated flush with the stomach and divided. Cut omental edges were divided to prevent leakage of the injection material. A nylon intravenous cannula (Portex) of appropriate size was then inserted into the artery to be injected and the accompanying vein left open. In one stomach the cannula was placed in the right gastroepiploic artery, but the left gastric artery and its arcade on the lesser curve were preserved. In 15 stomachs the cannula was placed in the right gastroepiploic artery after removal of all other vessels and in the remaining 2 stomachs the cannula was placed in the main trunk of the left gastric artery, with removal of all other vessels (*Fig.* 1).

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* Based on a communication to the Surgical Research Society, January 1978.

† Department of Surgical Studies, The Middlesex Hospital, London W1N 8AA.
Correspondence to: L. P. Le Quesne.

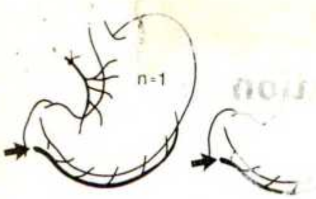

Fig. 1. Diagrammatic representa
performed with Chromopaque. The
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and (*c*) all the arteries to the stomach
the infusion, were removed after ligat
flush against the stomach wall.

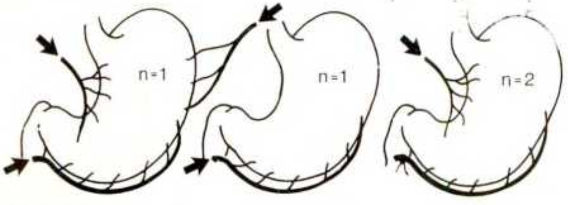


Fig. 2. Diagrammatic representation of the various infusions performed with resin. *See Fig.* 1 for explanation.

The stomach was next floated in a bath of 0·9 per cent saline solution and a small volume of air injected via the cannula to identify any leaks, which were sealed by further ligation. The nylon intravenous cannula was connected to the infusion apparatus for the injection of Chromopaque. The injection apparatus consisted of a pressurized bottle containing the injection medium, attached to a compressed air supply. The pressure within the system was maintained at 120–130 mmHg for a period of 3–6 min during the time of injection: this relatively high perfusion pressure was chosen to allow for the fact that many of the subjects were likely to have had systemic hypertension, as proved to be the case (*see Table I*). Injection was stopped when filling of the small serosal vessels was complete. After injection, the cannulated artery and the accompanying veins were ligated.

The intact stomach was then transferred to a Perspex board and a soft tissue radiograph taken using a Senographe CGR machine with CEA non-screen film and an exposure time of 1·5–1·7 s at 25 KV and 10 mA. After taking these films, the stomach was cut along the greater curve anterior to the epiploic arcade, except when the left gastric artery was injected, in which case the lesser curve was divided anterior to the left gastric arcade. The stomach was opened out and the serosal surface placed on the Perspex plate. Small vessel filling of the gastric mucosal vessels was assessed by naked eye examination and further X-rays were then taken.

In the two stomachs injected via the left gastric artery (*Fig.* 1*c*) the preparation was maintained at 37 °C during the injection of the Chromopaque medium, to which was added 10 per cent gelatin so that microangiography could be performed. After routine radiography, regions were selected for the microangiography. The selected area was arranged over a fine grain photographic plate (Ilford, EM5) and exposed by the same technique as above. The developed plates were then used to produce enlargements.

Resin cast technique (*4 stomachs*) (*Fig.* 2)

One stomach had a cannula placed in the right gastroepiploic artery, the left gastroepiploic artery and the left gastric artery with no ligation of vessels. Two stomachs had a cannula placed in the left gastric artery only, again with no ligation of other vessels while the remaining stomach had a cannula placed in the right gastroepiploic artery after removal of all other vessels. The stomachs were obtained and prepared for injection as already described. In some of the specimens the veins were also injected, with a different colour resin.

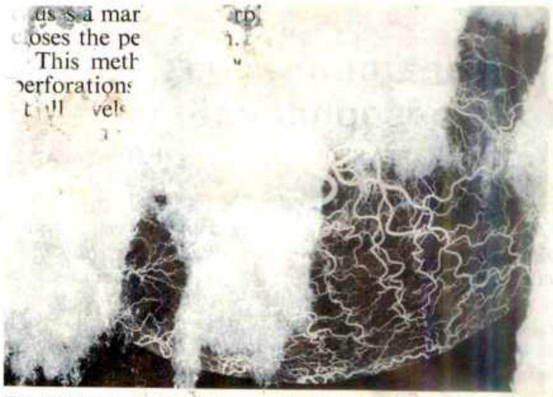


Fig. 3. Radiograph of a stomach following Chromopaqu
infusion via the right gastroepiploic artery (arrow) with
extragastric portion of the left gastric vessels intact (*Fi*
Note the good filling of the fundal vessels and also th
small calibre of the right gastric artery.

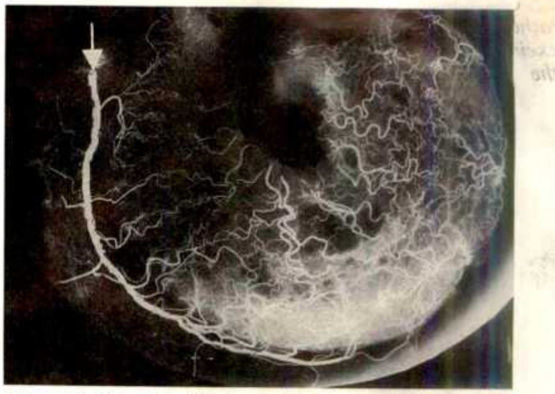


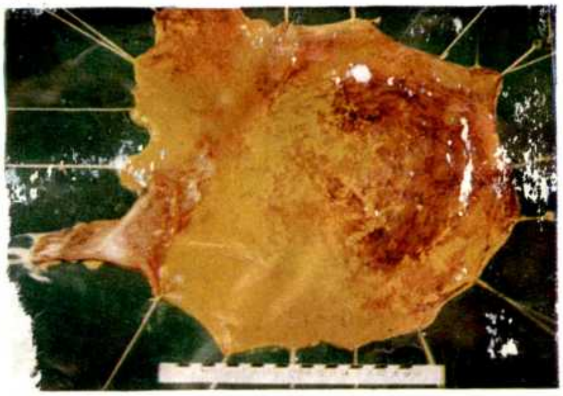
Fig. 4. Radiograph of a stomach following infusion via the right gastroepiploic artery (arrow), all the other gastric vessels having been removed (*Fig.* 1*b*). Note the good filling of the fundal vessels via intramural anastomotic channels.

A cold-setting polyester resin (Trylon CL 201 PA) was injected using a modification of Tompsett's technique (Tompsett, 1970). The mixture of constituents (resin, monomer, catalyst and pigment) was made up just before injection while still cold from the refrigerator. During the perfusion the stomach floated in a saline bath at room temperature, but after the injection the saline bath temperature was raised to 40 °C to accelerate the setting process. Following either tissue maceration in concentrated hydrochloric acid or tissue clearing by dehydration and immersion in methyl salicylate, the vascular patterns were examined.

Results

When the three main arteries (left gastric, right and left gastroepiploic) were injected, there was, as expected, good filling of the fundal vessels. Similarly, injection of the right gastroepiploic artery with the left gastric arcade intact produced good filling of both the arcade and the fundal vessels (*Fig.* 3).

When the right gastroepiploic artery alone was perfused after ligation of all other vessels flush with the stomach, filling of the fundal vessels was obtained both with the Chromopaque and resin techniques (*Fig.* 4). In 14 of the 16 studies the filling of the fundal vessels was comparable with that seen after the injections when the left gastric artery was intact; the



5. A stomach opened along the anterior wall after
on of Chromopaque into the right gastroepiploic artery,
er vessels having been removed (*Fig.* 1*b*). The yellow
opaque has filled the vessels of the body and fundus,
ng a corridor of poorly perfused tissue (pink in the
re) along the lesser curve.

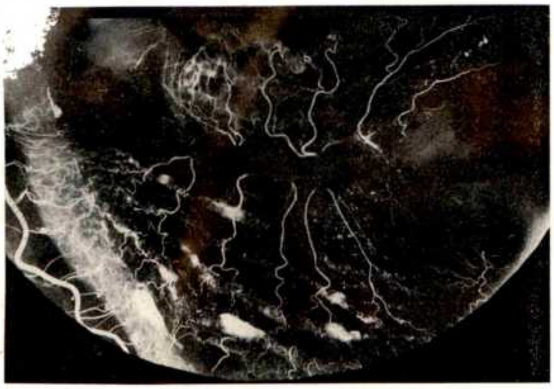


Fig. 6. Radiograph of a stomach opened along the greater curve after perfusion of Chromopaque via the right gastroepiploic artery (*Fig.* 1*b*). The avascular corridor along the lesser curve is clearly seen: this area of the stomach is supplied by the short branches of the left gastric artery, seen clearly in *Fig.* 8.

fundal vessels were seen to fill via the submucosal arterial plexus, although the lower oesophageal vessels undoubtedly filled better in the presence of the left gastric arcade. In the remaining 2 stomachs fundal filling was incomplete; in one this was due to technical errors and in the other there was marked atheroma of the main gastric arteries.

In the absence of the left gastric artery arcade the area least well filled was not the fundus of the stomach but the lesser curve of the stomach; this was true for all 16 stomachs examined in this manner. On opening the stomach, poor filling of the blood vessels of the lesser curve was obvious to the naked eye, leaving a corridor of poorly pigmented tissue, in sharp contrast to the yellow pigment easily seen in the body and, to a lesser extent, in the fundus of the stomach (*Fig.* 5). This avascular corridor along the lesser curve was also seen in radiographs of the opened stomach (*Fig.* 6). In those stomachs that were perfused via the left gastric artery after removal of all other vessels, no similar corridor was seen along the greater curvature.

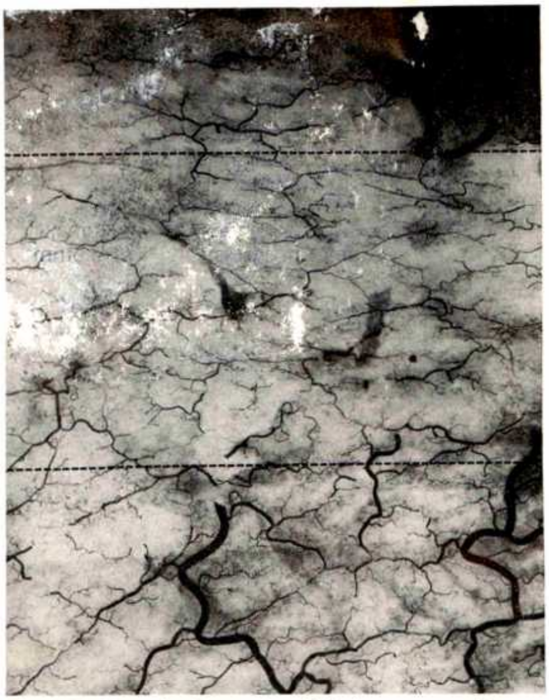


Fig. 7. Radiograph of a portion of the lesser curve of a stomach perfused with Chromopaque via the left gastric artery (*Fig.* 1*c*). The muscularis has been removed. The lesser curve lies across the centre of the picture, between the two dotted lines. On the anterior and posterior walls there is a free anastomosis between the submucosal vessels, whereas on the lesser curve anastomoses are fewer and end arteries are seen.

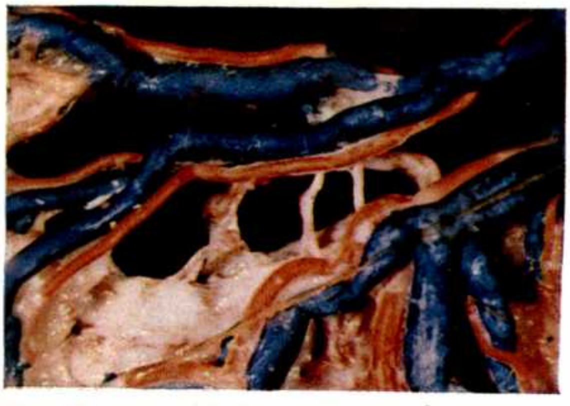


Fig. 8. Photograph of the lesser curve region of a stomach, after an infusion of resin into the left gastric artery (red) and vein (blue). The fat around the left gastric vessels together with the muscle coat of the stomach has been removed, to expose the submucous plane. In between the large branches running to the anterior and posterior walls of the stomach the smaller arteries running directly into the lesser curve can clearly be seen.

In order to examine the vascular pattern responsible for the corridor appearance on the lesser curve, areas of lesser curve were examined by microradiography and dissection. On the anterior and posterior walls there was a profuse anastomotic pattern of vessels fed from the main branches of the left gastric artery, while along the lesser curve itself a different pattern was apparent (*Fig.* 7). In this region the vessels were of smaller size, anastomoses were fewer and end arteries were noted, arising directly from the main branches of the left gastric artery and penetrating to the mucosa between the anterior and posterior leaves of the lesser omentum. These end arteries, which could be seen in the resin cast studies (*Fig.* 8), were present in the greatest numbers at the incisura angularis and became progressively less common proximally.

Discussion

In their meticulous study of the arterial supply of the human stomach, El-Eishi et al. (1973) clearly describe the distribution of the arteries supplying the stomach. But, whilst drawing attention to the many anastomoses in the gastric wall, they did not define the extent to which one artery could take over the territory normally supplied by another. This present investigation demonstrates that in an anatomical study the right gastroepiploic artery alone will perfuse the vessels in the fundus of the stomach, normally supplied by the left gastric artery. The perfusion of these vessels was found to be independent of the presence of the left gastric arcade and to occur through the submucosal anastomotic plexus. A feature of the injection pattern was the poor filling of the lesser curve vessels, which by microangiographic techniques was shown to be due to fewer intramural anastomoses.

Perfusion of the fundal vessels via the right gastroepiploic artery through the submucosal plexus has become important in the surgical management of oesophageal lesions with the realization that oesophagogastric anastomoses in the neck give rise to fewer and less dangerous problems than similar anastomoses in the thorax. Such an operation depends on the mobilization of the stomach into the neck without tension. It is currently recommended (McKeown, 1976) that the ligation of the left gastric artery at its origin is critical so that the gastric collateral branches are preserved, and the blood supply to the fundus secured. However, others have laid less emphasis on the integrity of the left gastric artery arcade (Akiyama et al., 1976). This study suggests that there is no anatomical basis for preservation of the left gastric arcade and that it can be removed without prejudice to the blood supply of the fundus of the stomach, provided that there is no significant atheroma of the right gastroepiploic artery. It should be noted, however, that an anatomical basis for fundal perfusion does not necessarily guarantee an adequate tissue blood flow. This purely *in vitro* study does not allow for the deformation and elongation which accompanies transposition of the stomach into the neck. However, the stomach is renowned for its ability to survive following ligation of many of its vessels, and it has been found that safety factors exist in the gastric circulation which allow a 60 per cent reduction in total gastric blood flow before an insufficiency of intracellular oxygen begins to limit cellular metabolism within the mucosa (Bowen et al., 1977). Thus, provided that the right gastroepiploic artery is not involved by atheromatous changes, it is likely that not only can this single vessel adequately perfuse the whole stomach, but that it can also do this in the absence of the extragastric arcade on the lesser curve. It is, however, to be noted that in the presence of severe atherosclerosis, transposition of the stomach may not be feasible even with the intact left gastric pedicle (Le Quesne and Ranger, 1966).

The end arteries noted on the lesser curve have been commented upon in previous studies on gastric vasculature (Reeves, 1920; Barlow et al., 1951; Piasecki, 1974), as has the decrease of the degree of anastomosis on the lesser curvature of the stomach (Piasecki, 1977). In no study, however, has the corridor effect been demonstrated after clearance of the lesser curve of the stomach. This area of poor filling is clearly related to the end arteries demonstrated in the resin casts and these arteries are sacrificed during proximal gastric vagotomy. This pattern of vascular supply probably explains the occasional occurrence of lesser curve necrosis following proximal gastric vagotomy (Johnston, 1975).

Acknowledgements

We are indebted to the late Professor R. D. Teare and Professor N. Woolf for allowing us access to the autopsy material on which this study was based. It is also a pleasure to express our thanks to the staff of the Department of Radiography and the Department of Physics for taking the radiographs, and to Mr R. Phillips and the staff of the Photographic Department for the illustrations.

References

AKIYAMA H., HIYAMA M. and HASHIMOTO C. (1976) Resection and reconstruction for carcinoma of the thoracic oesophagus. *Br. J. Surg.* **63**, 206–209.

BARLOW T. E., BENTLEY F. H. and WALDER D. N. (1951) Arteries, veins and arteriovenous anastomoses in the human stomach. *Surg. Gynecol. Obstet.* **93**, 657–671.

BOWEN J. C., DINESH K. and GARG B. S. (1977) Effect of graded mechanical ischaemia on oxygen tension and electrical potential in the canine gastric mucosa. *Gastroenterology* **73**, 84–88.

EL-EISHI H. I., AYOUB S. F. and ABD-EL-KHALEK M. (1973) The arterial supply of the human stomach. *Acta Anat.* **86**, 565–580.

JOHNSTON D. (1975) Operative mortality and postoperative morbidity of highly selective vagotomy. *Br. Med. J.* **4**, 545–547.

LE QUESNE L. P. and RANGER D. (1966) Pharyngolaryngectomy with immediate pharyngogastric anastomosis. *Br. J. Surg.* **53**, 105–109.

MCKEOWN K. C. (1976) Total three-stage oesophagectomy for cancer of the oesophagus. *Br. J. Surg.* **63**, 259–262.

PIASECKI C. (1974) Blood supply to the human gastroduodenal mucosa with special reference to the ulcer-bearing area. *J. Anat.* **118**, 295–335.

PIASECKI C. (1977) Role of ischaemia in the initiation of peptic ulcer. *Ann. R. Coll. Surg. Engl.* **59**, 476–478.

REEVES T. B. (1920) A study of the arteries supplying the stomach and duodenum and their relation to ulcer. *Surg. Gynecol. Obstet.* **30**, 374–385.

TOMPSETT D. H. (1970) *Anatomical Techniques*, 2nd ed. Edinburgh, Livingstone.

Paper accepted 24 October 1978.

.. gastric vagotomy on and gastric secretion

[illegible] (PC [illegible] rats [illegible] eloped [illegible] ine mea [illegible] 136 μmol/60 min [illegible] e was a significa[illegible] e in gastric juice [illegible] nd acidity ($P<0{\cdot}001$) with a fall in the mean [illegible] ated acid output to 12 μmol/60 min. On the [illegible] th day after vagotomy the stimulated acid out- [illegible] olume and concentration) significantly increased [illegible] μmol/60 min ($P<0{\cdot}001$). When the dose of [illegible] secretagogues was reduced by 50 per cent, a [illegible] on day 0 prevented any changes occurring in the [illegible] denal mucosa, but when repeated at 4 weeks after a [illegible] the severity of duodenal ulcers in vagotomized rats [illegible] greater than in those having had a sham operation [illegible] 0·05). This transient effect of a PGV on duodenal ulcerogenesis and gastric secretion may be due to recovery of the parietal cell mass.*

PROXIMAL gastric vagotomy (PGV) is being performed more frequently in the surgical treatment of chronic duodenal ulcer in man (Johnston, 1975; Kennedy et al., 1975; Kronborg and Madsen, 1975; Jordan, 1976). The operation of PGV preserves vagal innervation to the antrum and pylorus allowing adequate gastric emptying without the need for a drainage procedure. In spite of a decreased morbidity and mortality after a PGV compared with other operations for duodenal ulcer, there is an increasing incidence of recurrent peptic ulceration with each year of follow-up (Wastell and Zervos, 1976). The possible reasons for this recurrent ulceration after a PGV include an incomplete or inadequate vagotomy, regeneration of the transected vagal nerve fibres or reinnervation of the parietal cells by cholinergic nerves from the antrum.

A method of producing duodenal ulcers in rats by the infusion of gastric secretagogues has been previously described (Joffe, Gaskin et al., 1977). These ulcers appear to be similar to the duodenal ulcers found in man both morphologically and in their natural history (Gaskin et al., 1976). They can be prevented by various gastric antisecretory agents (Joffe et al., 1976; Joffe, Polak et al., 1977) and truncal vagotomy (Joffe and Ferrie, 1976). The aim of this study was to see the effect of a PGV on experimental duodenal ulcers in the rat with emphasis on the gradual recovery of the parietal cell mass after a proximal gastric vagotomy.

Materials and methods

Male albino Wistar rats were deprived of food for 18 h before operation but allowed free access to water.

Operative technique

After anaesthetic induction with ether, a 2-cm midline abdominal incision was made from the xiphisternum. Using a ×8 magnification (Mediscope, Mark II), the stomach was delivered into the wound and the oesophagogastric junction and the anterior neurovascular bundle were exposed. This bundle contained the left anterior vagus nerve, which innervated the body and rumen of the stomach anteriorly as well as the antrum and pylorus. The nerve supplying the antrum and pylorus arose proximal to the oesophagogastric junction and was easily isolated.

T[illegible] NUMBER OF RATS UNDERGOING A [illegible]IAL GASTRIC VAGOTOMY (PGV) OR SHAM [illegible]TION BEFORE INFUSION OF ULCEROGENIC [illegible]IC SECRETAGOGUES

[illegible]edure	Postoperative day 0	1	2	3	4	5	6	7	8	9	10	14	21	No. of rats
Operated														
PGV+P+C	8	8	8	8	8	8	8	8	8	8	8	8	8	104
PGV+saline	3	3	3	3	3	3	3	3	3	3	3	3	3	39
Sham+P+C	3	3	3	3	3	3	3	3	3	3	3	3	3	39
Unoperated														
Saline	3	3	3	3	3	3	3	3	3	3	3	3	3	39
P+C	3	3	3	3	3	3	3	3	3	3	3	3	3	39

P, pentagastrin (4 μg kg^{-1} min^{-1}); C, carbachol (0·8 μg kg^{-1} min^{-1}). PGV, proximal gastric vagotomy.

The posterior neurovascular bundle, which contained the right posterior vagus nerve, was exposed by reflecting the greater curvature of the stomach superiorly. Similarly, the vagal branch to the antrum arose above the oesophagogastric junction and could be easily isolated. These antral branches of the vagus in the rat are similar to the nerves of Latarjet which innervate the antrum in man, and these nerves can be clearly seen at the time of operation.

After identifying these vagal branches, two 5/0 silk ligatures were passed around the neurovascular trunks supplying the body and rumen anteriorly and posteriorly (*Fig.* 1). The neurovascular bundle was then divided between the ligatures and this denervated the body and rumen of the stomach but preserved the nerve supply to the antrum and pylorus. Haemostasis was achieved and the abdomen closed in layers using 2/0 silk for peritoneum and sheath and autoclips for skin. The sham operations consisted of laparotomy with identification and dissection of the vagal branches. The rats were weighed at 0900 h for 5 days preoperatively and then daily postoperatively. The animals were randomly allocated into two groups.

Group 1

A proximal gastric vagotomy was performed in 143 rats. Experiments were carried out on groups of rats immediately after operation and on each subsequent day until the tenth, and then again on the fourteenth and twenty-first days postoperatively. Using a Braun Unita I pump, a combination of two gastric secretagogues, pentagastrin (4 μg kg^{-1} min^{-1}) and carbachol (0·8 μg kg^{-1} min^{-1}) diluted to 18 ml with 150 mmol/l saline, was continuously infused subcutaneously into restrained rats for 24 h (Joffe, Gaskin et al., 1977).

On each of the postoperative days when the experiments were being performed, 3 sham and 3 unoperated rats were infused with gastric secretagogues and 3 unoperated rats were infused with saline, giving a total of 39 rats in each group (*Table I*). Immediately after the operation, and at 28 days postoperatively, a further group of 48 rats was infused with a 50 per cent dose of pentagastrin (2 μg kg^{-1} min^{-1}) and carbachol (0·4 μg kg^{-1} min^{-1}).

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* University Department of Surgery, Royal Infirmary, Glasgow.

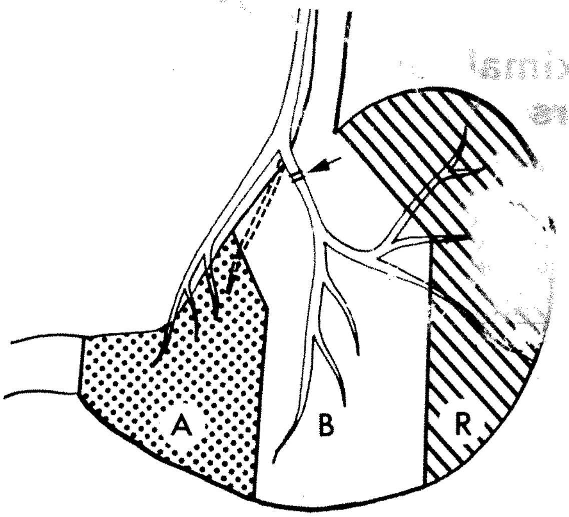

Fig. 1. Diagrammatic illustration of the trunk of the anterior vagus nerve dividing into the nerve to the antrum and pylorus (A) and the nerve to the rumen (R) and body of the stomach (B). The arrow represents the site of division of the branch of the anterior vagus nerve to the body and rumen of the stomach.

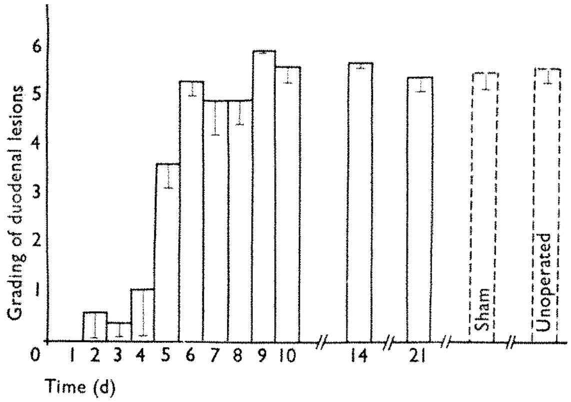

Fig. 2. Proximal gastric vagotomy and experimental duodenal ulcers: the influences of time after a proximal gastric vagotomy. The severity of duodenal lesions is graded semiquantitatively from 0 (normal) to 6 (penetrating or perforated duodenal ulcers).

At the end of the 24-h infusion the rats were killed using anaesthetic ether and a full laparotomy was carried out. The stomach and duodenum were opened along the greater curvature and antimesenteric surface respectively and then carefully inspected using a ×10 magnification lens for any duodenal lesion. The lesions were graded on a six-point scale of increasing severity by an observer who was unaware of the experimental conditions. Grade 0 was a normal mucosa, grade 1 oedema, grade 2 reddening of the mucosa, grade 3 petechiae, grade 4 erosions, grade 5 a definite ulcer crater and grade 6 penetrating or perforated duodenal ulcer.

Group 2

Gastric secretory tests were performed in sham-operated rats ($n = 30$) and PGV rats ($n = 30$) on day 0 and on the seventh postoperative day using a gastrostomy tube sutured into the rumen of the stomach for aspiration of the gastric contents (Joffe, Polak et al., 1977). The gastric juice was collected at 15-min intervals by gentle suction into 5-ml syringes and the volume measured. Following a 1-h basal period, pentagastrin (4 μg kg^{-1} min^{-1}) and carbachol (0·8 μg kg^{-1} min^{-1}) were subcutaneously infused and the gastric juice collected for a further 4 h. At the end of the 5-h experiment the acidity was determined by titrating against 0·1 N NaOH with phenol red as an indicator. The total acid output was expressed in μmol/60 min. Statistical analysis was carried out using Student's *t* test and the Mann–Whitney U test.

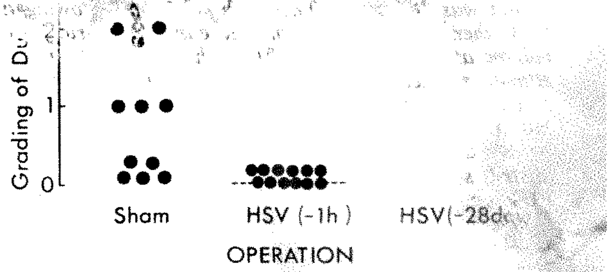

Fig. 3. The severity of duodenal lesions produced by a 24-h subcutaneous infusion of the gastric secretagogues pentagastrin (2 μg kg^{-1} min^{-1}) and carbachol (0·4 μg kg^{-1} min^{-1}) in sham-operated rats, immediately on recovery from a proximal gastric vagotomy (1 h) and 28 days after the PGV. The severity of duodenal lesions is graded from 0 (normal) to 6 (penetrating or perforated duodenal ulcers).

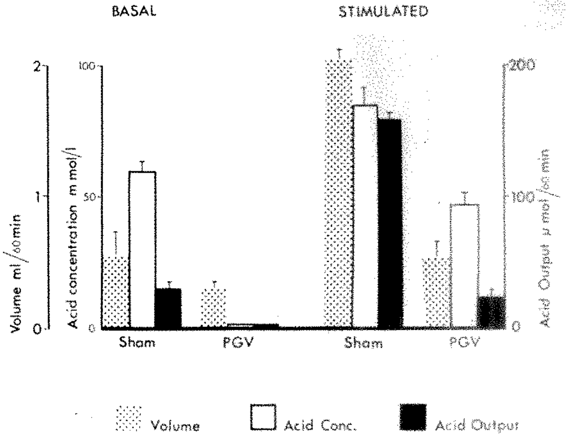

Fig. 4. Gastric secretory tests in rats after a sham-operation and immediately on recovery after a proximal gastric vagotomy (PGV) on day 0 (volume in ml/60 min, acid concentration in mmol/l and total acid output in μmol/60 min). Both basal and stimulated acid output after pentagastrin (4 μg kg^{-1} min^{-1}) with carbachol (0·8 μg kg^{-1} min^{-1}) are shown.

Results

During this study none of the rats died. The mucosa of the stomach and duodenum in unoperated rats and

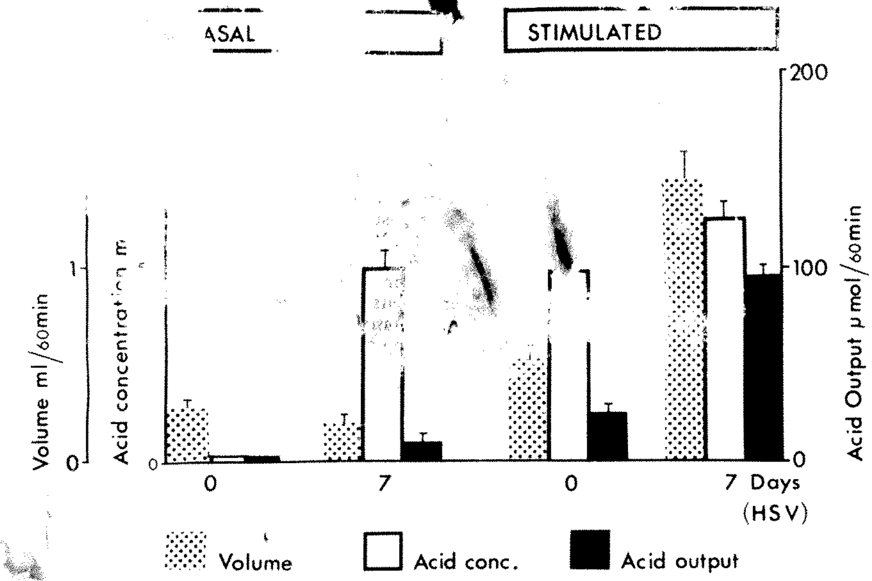

Fig. 5. Gastric secretory tests in rats immediately on recovery after a proximal gastric vagotomy on day 0 and 7 days postoperatively (volume in ml/60 min, acid concentration in mmol/l and total acid output in µmol/60 min). Both basal and stimulated acid output after pentagastrin (4 µg kg^{-1} min^{-1}) with carbachol (0·8 µg kg^{-1} min^{-1}) are shown.

in PGV rats after a 24-h infusion of saline was normal (grade 0). Pentagastrin and carbachol produced a 100 per cent incidence of duodenal ulceration in sham-operated and unoperated rats. The effect of the gastric secretagogues in vagotomized rats is shown in *Fig.* 2. Pentagastrin and carbachol had virtually no effect on the duodenal mucosa from day 0 to day 3 after a PGV. However, on day 4 there was evidence of a penetrating duodenal ulcer in 1 of the 8 rats infused with the gastric secretagogues. The remaining rats had a normal duodenal mucosa. By day 5, 3 out of 8 rats had a duodenal ulcer and this secretagogue-induced duodenal ulceration was consistently present on days 7, 8, 9, 10, 14 and 21 after a PGV (*Fig.* 2).

When rats were subcutaneously infused with 50 per cent of the ulcerogenic dose of gastric secretagogues for 24 h, sham-operated rats developed a wide range of changes in the duodenal mucosa. This varied from being macroscopically normal to duodenal ulceration with perforation. The mean severity of the duodenal lesions in this group was 2·6 (*Fig.* 3). A proximal gastric vagotomy followed immediately on recovery by an infusion of this half-dose of gastric secretagogues totally prevented any changes in the duodenal mucosa (grade 0). However, when the same experiments were repeated 4 weeks after a PGV, there was a significant increase in the duodenal lesions produced ($P<0{\cdot}05$) and all the rats developed either duodenal erosions ($n = 3$) or duodenal ulcers ($n = 9$) (*Fig.* 3).

In sham-operated saline-infused rats the mean BAO was 33 µmol/60 min and after secretagogue stimulation the BAO was significantly increased to a mean of 186 µmol/60 min ($P<0{\cdot}001$). After recovery from a proximal gastric vagotomy (day 0), the basal volume of gastric juice was 0·27 ml/60 min and the fluid was achlorhydric. On stimulation with gastric secretagogues, there was an increase in these PGV rats in both volume and acidity and acid output increased to a mean of 12 µmol/60 min (*Fig.* 4).

In the PGV rats on day 7 there was a significant increase in gastric juice volume after secretagogue stimulation ($P<0{\cdot}001$) and in acidity ($P<0{\cdot}001$) of the gastric juice when compared with the early postoperative results (*Fig.* 5). The gastric secretory tests performed in the sham-operated rats 1 week postoperatively did not differ significantly from the results obtained immediately after operation ($P>0{\cdot}1$).

Discussion

In this study a proximal gastric vagotomy has been shown to have a temporary inhibitory effect on experimental duodenal ulcers. From the sixth postoperative day all the rats developed duodenal ulcers after a subcutaneous infusion of ulcerogenic doses of gastric secretagogues regardless of the PGV. There are several possible explanations for this change in responsiveness of the gastric parietal cells to the infusion of pentagastrin and carbachol.

The recurrent peptic ulceration in man and the increase in acid output with time in response to insulin seen after a proximal gastric vagotomy may be due to vagal nerve regeneration or 'sprouting'. The changes found in these animal experiments, however, occurred too early in the postoperative period for this process to have occurred. Furthermore, histological staining of nerve tissue and electron microscopy of gastric mucosa from rats undergoing a truncal vagotomy shows nerve degeneration of the vagal fibres innervating the parietal cells on postoperative days 4, 7, and 11 (Kalabanis et al., 1974).

If the formation of duodenal ulcers in unoperated or sham-operated rats is due to the combined actions of pentagastrin, carbachol and a normal vagal tone, then in vagotomized rats the total stimulus to acid secretion would be less. Initially, the reduced stimulus would be inadequate to produce duodenal ulceration. With the recovery of the parietal cell sensitivity, however, the reduced stimulus becomes adequate, causing the peptic ulceration. The increase in both the basal and stimulated gastric acid output on the seventh postoperative day would tend to support this. The duodenal lesions produced by infusing half the dose of gastric secretagogues over 24 h also indicated a change in the responsiveness of the gastric parietal cells. On day 28 following a PGV all the rats developed either duodenal erosions or ulceration compared with the duodenal changes in sham-operated rats (grade 2·6) or the normal duodenal mucosa found in rats after a PGV followed immediately by an infusion of a 50 per cent dose of gastric secretagogues. The supposition that there is an early return of gastric secretory cell sensitivity after vagal denervation seems defensible.

An alternative hypothesis is that the duodenal ulceration is due entirely to the pentagastrin and carbachol administered and that vagotomy inhibits for several days the effect of these gastric secretagogues. This mechanism involves assumptions for which there is no collaborative evidence. In view of the period of decreased sensitivity to stimulation being so brief, it may well be a non-specific effect of the operation rather than a direct consequence of the vagotomy. The stimulant regimen might be so powerful as to be unaffected by vagotomy and the transient postoperative insensitivity could be due to ischaemia resulting from the inevitable devascularization of the proximal stomach during the vagotomy.

There have been several reports indicating a change in responsiveness of the parietal cell to stimulation after a proximal gastric vagotomy, without any adequate explanation for the effect. Amdrup and Griffith carried out experiments in dogs with Heidenhain pouches 3–4 weeks after a PGV (Amdrup and Griffith, 1970). Although there was no change in the fasting Heidenhain pouch secretion, there was a significant rise in the 24-h gastric output in response to food. Hirschowitz et al. (1976) also found changes in cholinergic receptors in dogs after a proximal gastric vagotomy.

It is entirely possible that the effect of the operation is due to ischaemia resulting from the inevitable devascularization which occurs during the PGV. Further work is necessary to determine the more precise caus[illegible] rec[illegible] of the secreto[illegible] in the stoma[illegible] afte[illegible] [illegible]mal gast[illegible]

References

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BA[illegible]AT R. [illegible]KRIE M. M. and [illegible] simple technique for gastric parietal [illegible] vagotomy in the rat. *Experientia* **33**, 1254–1255.

[illegible]SKIN R. [illegible]GAD A., BARROS D'SA A. A. J. et al. (1976) Natural history and morphology of secretagogue-induced duodenal ulcers in rats. *Gastroenterology* **69**, 903.

HIRSCHOWITZ B. I., OLSON R., WRIGHT L. et al. (1976) Changed cholinergic receptor characteristics after vagotomy in gastric fistula dogs. *Am. J. Physiol.* **230**, 105–109.

JOFFE S. N. and FERRIE M. M. (1976) Vagotomy and experimental duodenal ulcers. *Acta Hepatogastroenterol.* **23**, 435–440.

JOFFE S. N. and FERRIE M. M. (1977) The effect of GIH and Boots secretin and cholecystokinin on duodenal ulcers in the rat. *Acta Hepatogastroenterol.* **24**, 458–461.

JOFFE S. N., GASKIN R., BARROS D'SA A. A. J. et al. (1976) Prevention of secretagogue-induced ulcers in the rat. *Gastroenterology* **70**, 751–752.

JOFFE S. N., GASKIN R. J., BARROS D'SA A. A. J. et al. (1977) Secretagogue-produced duodenal ulcers in the rat. *Br. J. Surg.* **64**, 218–220.

JOFFE S. N., POLAK J. M., PALLONE F. et al. (1977) Gastrin, antral G cells and gastric acid in secretagogue-induced and antihistamine-inhibited duodenal ulcers. *Scand. J. Gastroenterol.* **12**, 27–32.

JOHNSTON D. (1975) Operative mortality and postoperative morbidity of highly selective vagotomy. *Br. Med. J.* **4**, 545–547.

JORDAN P. H. (1976) Parietal cell vagotomy without drainage for treatment of duodenal ulcer. *Arch. Surg.* **111**, 370–376.

KALABANIS N. G., NYHUS L. M. and DAS GUPTA T. K. (1974) Morphologic evidence of direct innervation of parietal cells in rodent gastric mucosa. *Surg. Forum* **25**, 333–335.

KENNEDY T., JOHNSTON G. W., MACRAE K. D. et al. (1975) Proximal gastric vagotomy: interim results of a randomized control trial. *Br. Med. J.* **2**, 301–303.

KRONBORG O. and MADSEN P. (1975) A controlled, randomized trial of highly selective vagotomy versus selective vagotomy and pyloroplasty in the treatment of duodenal ulcers. *Gut* **16**, 268–271.

WASTELL C. and ZERVOS G. N. (1976) Proximal gastric vagotomy (PGV): 100 patients with up to 7 years follow-up. *Excerpta Medica* **389**, 124.

Paper accepted 11 September 1978.

[illegible] pyloroplasty for gastric ulcers

[illegible] D M. [illegible] AR*

[illegible] gas[illegible] [illegible]ated by [illegible] a dis[illegible] general hospital [illegible] were re[illegible] postoperative deaths in the patien[illegible] surgery but 8 deaths in those [illegible] emergency surgery for massive bleedin[illegible]). Eighty-three per cent of patients had a [illegible] was classed as good or satisfactory. Recurrent gastric ulceration was found in 8 per cent and a tendency to late asymptomatic ulcer recurrence is identified. Careful long term follow-up, including endoscopic re-examination, is advocated for patients undergoing conservative operations for benign gastric ulcer.

In recent years there has been a move towards less radical surgery in many fields. In keeping with this trend and encouraged by previous experience and enthusiastic reports (Farris and Smith, 1963; Dorton, [illegible]: Hendry and Bahrani, 1965; Burge, 1966; Kraft et al., 1966; McNeil et al., 1969; Burge et al., 1970; Daniels and Strachan, 1973), 80 patients with proved benign chronic gastric ulcers have been treated by vagotomy and pyloroplasty in a district general hospital. This study reports the results of those operations.

Patients and methods,

The records of all 80 patients with benign gastric ulcers treated surgically by vagotomy and pyloroplasty during the period January 1971 to November 1975 in a district general hospital were reviewed. There were 60 surviving patients of whom 44 were personally interviewed by one author (M. C. E.). Information was obtained from general practitioners on a further 9 and 7 were lost to follow-up.

At interview, each patient's symptoms were graded according to a modified Visick scale (Duthie et al., 1970). A routine follow-up endoscopic examination was planned in all cases but this was contraindicated in 9 asymptomatic patients on medical grounds or because of age. Hence, 35 patients were invited to attend for a follow-up endoscopic examination and 28 of these accepted. These examinations were carried out as outpatient procedures by one author (M. C. E.) and included gastric mucosal biopsy in all cases.

Three-quarters of the patients in this study were under the care of one of the authors (M. W. L. G.) and in most of these cases a standard management protocol was followed, which included a preoperative endoscopic examination with tissue sampling for both cytological and histological assessment, an operative biopsy of the gastric ulcer for frozen section and also subsequent paraffin section histology, and, finally, a postoperative endoscopic examination several months later. The remaining patients were under the care of two other consultant general surgeons and no single management protocol was used in these cases.

Table I shows the extent to which the standard protocol was followed. The surgery involved truncal vagotomy in 46 cases and selective vagotomy in the other 34. The pyloroplasty was of the Heinicke–Mickulicz type in all cases.

The cases were subdivided into groups representing the three types of gastric ulcer—type I gastric ulcer, type II combined gastric and duodenal ulcer and type III prepyloric gastric ulcer (Johnson, 1965)—based on the site of the ulcer and the presence or absence of duodenal ulceration as shown on endoscopic and/or operative findings.

The recurrence rate and symptomatic results were assessed for each type of gastric ulcer separately. All results were tested for significance using the exact test for 2×2 contingency tables (Bailey, 1959).

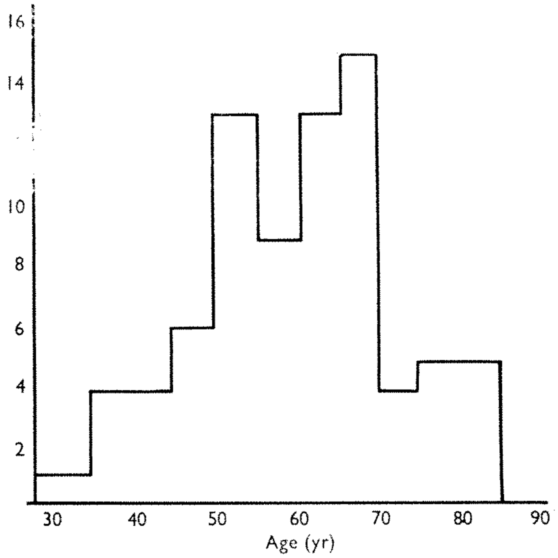

Fig. 1. Age distribution of 80 patients in this study.

Results

The study consists of 80 patients—49 male and 31 female—with an age distribution as shown in *Fig.* 1. In 59 patients surgery was undertaken electively for the standard surgical indications. There were no postoperative deaths in this group. The remaining 21 patients were operated on for massive or continuing bleeding and there were 8 postoperative deaths (38 per cent) in this group.

The patients were subdivided according to the type of gastric ulcer and *Table II* shows the numbers in each group. Twenty patients have died since surgery from a variety of causes, as shown on *Table III*, and a further 7 were lost to follow-up. The remaining 53 have all been followed for at least 2 years, with an average follow-up of 4·2 years. Sixteen of the 18 patients operated on 5 or more years ago had complete follow-up information. *Table IV* shows the modified Visick grading for those 54 patients with adequate follow-up. This group included 44 patients having elective surgery and 10 patients having emergency surgery for bleeding. Seventy-four per cent of this group had a good result (Visick 1 and 2), 9 per cent a satisfactory result (Visick 3) and 17 per cent a poor result (Visick 4 and 5). *Table V* shows the modified Visick grading in those 44 patients having elective surgery. A good result was achieved in 79·5 per cent, a satisfactory result in 4·5 per cent and a poor result in 16 per cent. These results do not differ significantly from those obtained after emergency surgery.

Tables IV and *V* also show the modified Visick grading when the patients are subdivided according to ulcer type. There were no significant differences in

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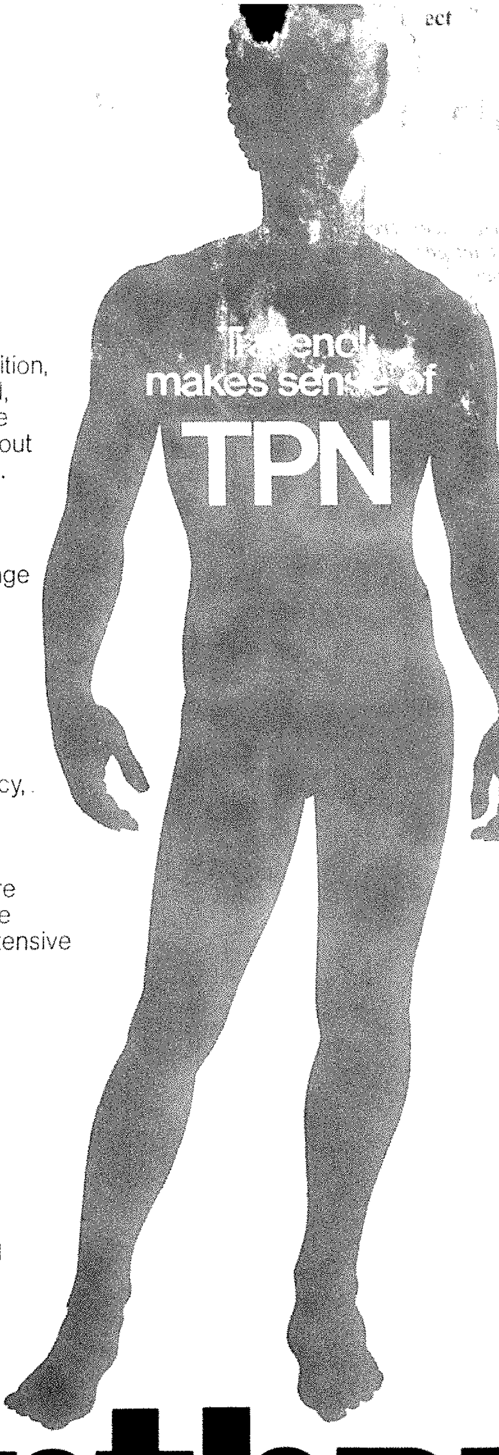

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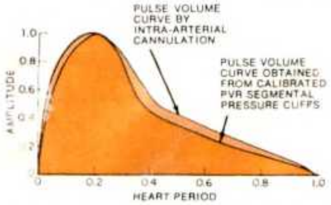

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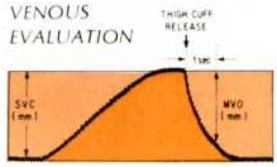

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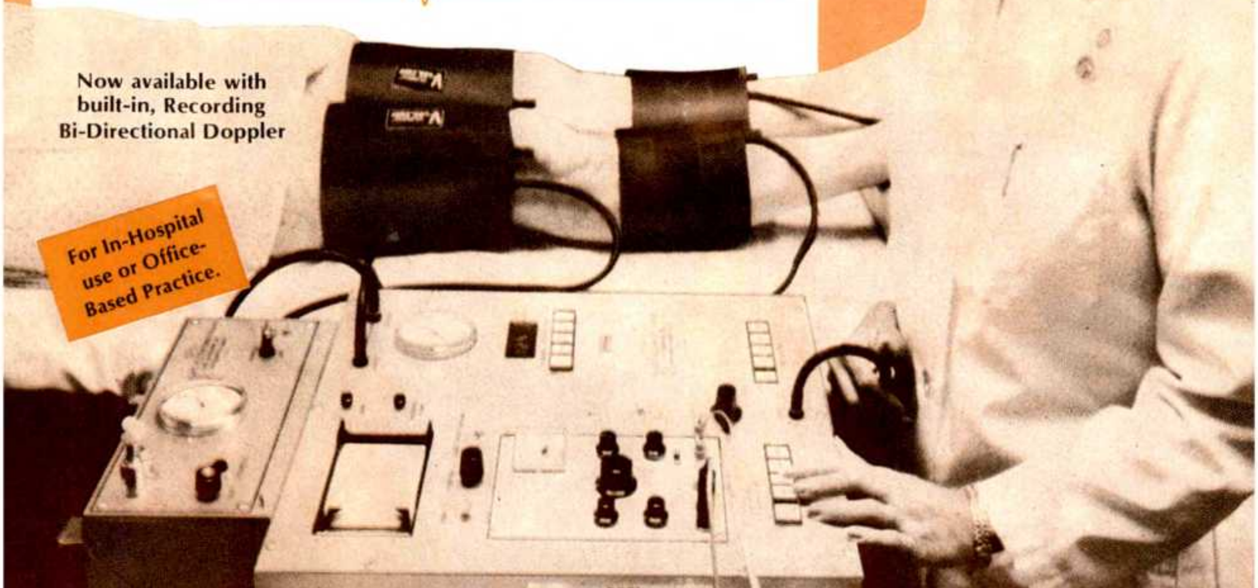

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	ΔP_S			PVR			Post Exercise		Exercise Symptoms
	Arm-Thigh	Thigh-Calf	Calf-Ankle	Thigh	Calf	Ankle	P_S Ankle† (mmHg)	PVR Category	
A-I Stenosis ODS	YES	NO	NO	ABN	ABN	ABN	<50	5 (quick recovery)	Calf, Thigh, Buttocks
A-I Occlusion ODS	YES	NO	NO	ABN	ABN	ABN	<20	5	Calf, Thigh, Buttocks
SFA Occlusion (Low) No A-I Disease*	NO	YES	YES	NOR	ABN	ABN	20-50	4	Calf
SFA Occlusion (High) No A-I Disease*	YES	YES	YES	ABN	ABN	ABN	20-50	4	Calf, Lower Thigh
Combined Disease A-I + SFA	YES	YES	YES	ABN	ABN	ABN	<10	5	Calf, Thigh, Buttocks
Tibial Vessel Disease	NO	NO	YES	NOR	NOR	ABN	30-70	4	Foot, Ankle, Calf
Small Vessel Disease	NO	NO	NO	NOR	NOR	NOR**	—	—	—

A-I — *Aorto-iliac.* **ODS** — *Open Distal System.* **SFA** — *Superficial Femoral Artery.* * — *No Hemodynamically Significant A-I Disease Present.* † — *Values quoted are not absolute and are given as a guide.* ΔP_S —*Systolic Pressure Difference.* **ABN** — *Abnormal.* **NOR** — *Normal.* ** — **PVR** *recordings at transmetatarsal region and/or digits reduced.* P_S — *Systolic Pressure.*

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Visick grading or ulcer recurrence between type I [illegible] types II and III gastric ulcers.

Table VI shows the modified Visick grading befo[illegible] endoscopic examination for all 44 patients interview[illegible] divided according to whether or not they had an endoscopic examination. The 16 patients who were not examined all had a good (Visick 1 and 2) or satisfactory (Visick 3) result. Of the remaining 28 patients, 71·5 per cent had a good result, 18 per cent a satisfactory result and 10·5 per cent a poor result. The difference between these two groups was not statistically significant. The 9 poor results represent 4 recurrent gastric ulcers proved at endoscopy, 1 recurrent gastric ulcer proved at post-mortem, 1 patient requiring reoperation for obstruction and 3 patients with severe post-vagotomy symptoms.

Three cases of extensive gastric carcinoma presented at 2 years 7 months, 2 years 11 months and 3 years 3 months respectively after surgery. A fourth case of peritoneal carcinomatosis of undetermined primary site presented at 6 years after surgery. There was 1 case of 'ulcer-cancer' and 1 case of an incidental finding of leiomyoblastoma of the stomach.

Discussion

The accepted standard surgical treatment for benign gastric ulcer is Billroth I gastrectomy. This operation has given good results but is by no means ideal (Louw and Marks, 1977). The operative mortality may be low in specialized units but the accepted world mortality rate is of the order of 2 per cent (Baron and Spencer, 1976; Johnston and Goligher, 1976) and may reach 4–5 per cent even in good units (Louw and Marks, 1977). The reported recurrence rate is at least 2 per cent and may reach 4–6 per cent (Johnson and Judd, 1971; Duthie and Kwong, 1973; Neilsen et al., 1973). There is also a significant minority of patients who develop substantial post-gastrectomy syndromes.

The lower operative mortality of vagotomy and drainage of about 1 per cent (Baron and Spencer, 1976; Johnston and Goligher, 1976) and its proved ability to heal gastric ulcers (Dragstedt et al., 1944; Farris and Smith, 1963; McNeil et al., 1969; Burge et al., 1970; Duthie et al., 1970) have led a number of surgeons to use this operation in the surgical treatment of benign gastric ulcers. The reports of this treatment have ranged from enthusiastic (Burge, 1966) to pessimistic (Stemmer et al., 1968). Many series have reported a low operative mortality, a recurrence rate after surgery of about 5 per cent and symptomatic results comparable to those obtained with Billroth I gastrectomy (Burge et al., 1970; Clarke et al., 1972; Kennedy et al., 1972; Johnston and Goligher, 1976).

These results prompted Duthie and co-workers to report a controlled prospective trial of vagotomy and pyloroplasty versus Billroth I gastrectomy in the surgical treatment of benign gastric ulcers. They found a recurrence rate of 10 per cent after vagotomy and pyloroplasty and 4 per cent after Billroth I gastrectomy (Duthie and Kwong, 1973). There were no operative deaths in either group but significantly greater operative morbidity occurred after Billroth I gastrectomy. This was partly offset by an early symptomatic superiority of gastrectomy (Duthie et al., 1970) which, however, was not maintained with longer follow-up (Duthie and Kwong, 1973). These authors concluded that vagotomy and pyloroplasty was a satisfactory operation for gastric ulcer when there were reasons for avoiding gastrectomy, but their trial produced no evidence that vagotomy and pyloroplasty should replace gastrectomy as the operation of choice.

[illegible] STANDARD

	%
Preope[illegible] [illegible]mination ($n = 80$)	67·5
Operati[illegible]	60
Postoperati[illegible] [illegible]ic examination ($n = 72$)	51

Table II: SUBDIVISION O[illegible] ACCORDING TO ULCER TYPE

	All patients	Emergency operations
Type I: gastric ulcer	58	15
Type II: combined gastric and duodenal ulceration	16	5
Type III: prepyloric ulcer	6	1
Total	80	21

Table III: CAUSE OF DEATH IN PATIENTS WHO HAVE DIED SINCE OPERATION

	No.
Postoperative death	8
Carcinoma of the stomach	2
Peritoneal carcinomatosis (unknown primary site)	1
Retroperitoneal sarcoma	1
Unrelated death	[illegible]
Total	[illegible]

Table IV: MODIFIED VISICK GRADING ACCORDING TO ULCER TYPE FOR ALL OPERATIONS

	Good (1 and 2)	Satisfactory (3)	Poor (4 and 5)
All patients ($n = 54$)	74	9	17
Type I gastric ulcers ($n = 39$)	72	10	18
Type II and III gastric ulcers ($n = 15$)	80	7 (1)	13 (2)

All figures are percentages.

Table V: MODIFIED VISICK GRADING ACCORDING TO ULCER TYPE FOR ELECTIVE OPERATIONS

	Good (1 and 2)	Satisfactory (3)	Poor (4 and 5)
All patients ($n = 44$)	79·5	4·5	16
Type I gastric ulcers ($n = 31$)	77·5	6·5	16
Type II and III gastric ulcers ($n = 13$)	84·5	0	15·5 (2)

All figures are percentages.

Table VI: MODIFIED VISICK GRADING OF THE 44 PATIENTS INTERVIEWED ACCORDING TO WHETHER OR NOT THE PATIENT HAD AN ENDOSCOPIC EXAMINATION

	Good (1 and 2)	Satisfactory (3)	Poor (4 and 5)
No examination ($n = 16$)	93·75	6·25 (1)	0
Endoscopic examination ($n = 28$)	71·5	18	10·5 (3)

All figures are percentages.

The situation is much less controversial when emergency surgery for a bleeding gastric ulcer is conside [illegible] Several authors have reported mortality rates [illegible] vagotomy and pyloroplasty with under-running [illegible] the bleeding vessel which are approximately half thos[illegible] obtained with emergency gastrectomy (Esselstyn, 1976; Johnston and Goligher, 1976), yet with no significant differences in rebleeding rates (Esselstyn, 1976). The results in this study are very much in accord with the preceding ones. There were no operative deaths among the 59 patients having elective operations, but there were a disturbing 8 deaths among the 21 having emergency operations for bleeding (38 per cent). There were 5 proved recurrent gastric ulcers in the 65 patients who have been fully followed up (8 per cent). The modified Visick grading of symptoms of 54 patients (*Table IV*) showed that 74 per cent had a good result, 9 per cent were satisfactory and 17 per cent poor. These results include 10 patients who had emergency surgery for massive blood loss but the results are not significantly different if these emergency cases are excluded (*Table V*).

Several authors (Kennedy et al., 1972; Duthie and Kwong, 1973; Douglas and Duthie, 1971) have reported much better results when vagotomy and drainage is used to treat type II and III gastric ulcers than when it is used to treat type I ulcers. Duthie believes the inclusion of type II and III gastric ulcers in studies of gastric ulcers treated by vagotomy and pyloroplasty favourably biases the results of surgery and he feels this may explain some of the wide variations in the results. However, we have not been able to confirm this in our study. There were 4 recurrent ulcers in 50 type I gastric ulcers (8 per cent), with 72 per cent having a good symptomatic result, and 1 recurrence in 15 type II and III gastric ulcers (7 per cent), with 80 per cent having a good symptomatic result. These differences are not significant.

One gastric ulcer recurred 13 months after surgery but the remaining 4 recurrent ulcers all presented 5 or more years later. This gave a recurrence rate of 22 per cent in the 18 patients operated on at least 5 years ago. This feature of late recurrence has been observed by other authors (Stemmer et al., 1968). They reported 5 recurrent ulcers in 18 patients (36 per cent) treated by vagotomy and drainage presenting at a mean of 5·2 years after surgery.

In the present study the striking feature of these late recurrent ulcers was the virtual absence of symptoms. Two patients were entirely asymptomatic and were found to have recurrent ulcers at follow-up endoscopy, 1 patient had vague abdominal discomfort which was not suggestive of recurrent ulceration and the fourth presented with a massive gastrointestinal bleed having had no premonitory symptoms. Four of these 5 patients with recurrent ulcers were re-examined endoscopically a few months after their original operation and in all cases the original gastric ulcer was seen to have healed. It is of interest that 28 patients in this series agreed to endoscopic re-examination and 3 recurrent gastric ulcers were found, all in patients who had had their operation at least 5 years previously.

These late asymptomatic recurrent ulcers indicate that careful follow-up of patients, including endoscopic re-examination, is necessary. Ideally these patients should be re-examined at yearly intervals, but this poses considerable practical problems. In addition to any logistic problems, there is the difficulty [illegible]f long term follow-up in a continually ageing popula[illegible]on. In this study a routine endoscopic re-examina[illegible]n was considered to be contraindicated in asympto[illegible]ic patients over 75 years of age and in those with [illegible]cal conditions such as recent ischaemic chest pain. [illegible]asonable compromise would be to follow all [illegible] annually in the outpatients department and [illegible]ne endoscopically those developing symptoms [illegible] haemoglobin concentration.

[illegible]udy 3 patients presented with extensive [illegible]r at a mean of 2 years 11 months after [illegible]ll have subsequently died. A further [illegible]ed with peritoneal carcinomatosis of un[illegible]ed primary site 6 years later. Three of these 4 patients had preoperative and operative tissue sampling without evidence of malignancy and postoperative endoscopic examination confirmed healing of the gastric ulcer.

The absence of any evidence of malignancy on tissue sampling, the observed healing of the ulcer and the time interval of well over 2 years between surgical treatment of the original ulcer and the presentation with gastric cancer suggest that these cases represent 'new' rather than 'missed' cancers.

There was one case of true 'ulcer-cancer'; this man had a microscopic focus of malignancy within a benign gastric ulcer. This was detected on paraffin section histology having been overlooked on frozen section histology. He had a Polya gastrectomy and has remained well without recurrent tumour. This case serves to illustrate that conservative surgery for gastric ulcers must be undertaken with great care to avoid missing potentially curable ulcer-cancers. The use of endoscopic examination including tissue sampling for both histological and cytological assessment has achieved a high but not complete level of accuracy (Gear and Rocyn-Jones, 1977). In this study there were two instances of endoscopic biopsy material reported as containing malignant tissue and two reports of malignant cells seen in cytological specimens, yet in each case no evidence of malignancy was detected at operation or on an operative specimen. All 4 patients have since remained well for an average of 4 years. This reinforces the need to obtain adequate operative biopsy specimens to confirm an endoscopic diagnosis. No cases of early gastric cancer were detected in the 28 follow-up endoscopic examinations. In all cases multiple gastric mucosal biopsies were taken and it is planned to report the mucosal changes detected in a subsequent paper.

In conclusion, this study confirms that there will be a 'good' or 'satisfactory' result in over 80 per cent of patients with benign gastric ulcer treated by vagotomy and pyloroplasty. However, the number of asymptomatic late recurrent ulcers raises the question about the long term efficacy of the operation. It appears from this study and previous reports that this operation is particularly indicated in those patients with type II and III ulcers; it should also be used when there are reasons for avoiding a gastrectomy, such as a potentially technically hazardous operation in a frail patient or in one with a substantial risk of postgastrectomy syndrome and as emergency surgery for a bleeding ulcer. The tendency towards late, asymptomatic ulcer recurrence and the cases developing gastric cancers reported in this study raises a note of caution and implies a prolonged follow-up period with endoscopic re-examination where appropriate. The results of current trials using highly selective vagotomy in the treatment of benign gastric ulcer are awaited with interest.

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References

BAILEY N. T. J. (1959) *Statistical Methods in Biology*. London, English University Press.

BARON J. H. and SPENCER J. (1976) Facts and heresies about vagotomy. *Surg. Clin. North Am.* 56, 1297–1312.

BURGE H. (1966) The aetiology of benign lesser curve gastric ulcer: vagotomy and pyloroplasty in its treatment. *Ann. R. Coll. Surg. Engl.* 38, 349–369.

BURGE H., MORTON G. A., MACLEAN C. et al. (1970) Four-year to eight-year results of vagotomy and simple drainage for benign lesser curve gastric ulcer. *Br. Med. J.* 3, 376–378.

CLARKE R. J., LINCOLN LEWIS D. and ALEXANDER-WILLIAMS J. (1972) Vagotomy and pyloroplasty for gastric ulcer. *Br. Med. J.* 2, 369–371.

DANIELS H. A. and STRACHAN A. W. B. (1973) Gastric ulcer treated by vagotomy, pyloroplasty and ulcerectomy. *Br. J. Surg.* 389–391.

DORTON E. D. (1964) Vagotomy and pyloroplasty for gastric ulcer. *Am. Surg.* 30, 561–565.

DOUGLAS M. C. and DUTHIE H. L. (1971) Vagotomy for gastric ulcer combined with duodenal ulcer. *Br. J. Surg.* 58, 721–724.

DRAGSTEDT J. R., PALMER W. L., SHAFER P. W. et al. (1944) Supradiaphragmatic section of the vagus nerves in the treatment of duodenal and gastric ulcers. *Gastroenterology* 3, 450–462.

DUTHIE H. L. and KWONG N. K. (1973) Vagotomy or gastrectomy for gastric ulcer. *Br. Med. J.* 4, 79–81.

DUTHIE H. L., MOORE K. T. H., BARDSLEY D. et al. (1970) Surgical treatment of gastric ulcers: controlled comparison of Billroth I gastrectomy and vagotomy and pyloroplasty. *Br. J. Surg.* 57, 784–787.

ESSELSTYN C. B. Jun. (1976) Surgical management of actively bleeding duodenal ulcers. *Surg. Clin. North Am.* 56, 1387–1393.

FARRIS J. M. and SMITH G. K. (1963) The treatment of gastric ulcer (*in situ*) by vagotomy and pyloroplasty. *Ann. Surg.* 158, 461.

GEAR M. W. L. and ROCYN-JONES J. (1977) A study of the accuracy of endoscopic biopsy and cytology. (Unpublished).

HENDREY G. W. and BAHRANI A. I. Z. (1965) Gastric ulcer and conservative surgery. *Br. J. Surg.* 52, 588–596.

JOHNSON C. L. and JUDD E. S. (1971) The usefulness of vagotomy in treatment of gastric ulcer. *Surg. Clin. North Am.* 51, 907–914.

JOHNSON H. D. (1965) Gastric ulcer classification, blood group characteristics, secretion patterns and pathogenesis. *Ann. Surg.* 162, 996–1004.

JOHNSTON D. and GOLIGHER J. C. (1976) Selective, highly selective or truncal vagotomy. *Surg. Clin. North Am.* 56, 1313–1331.

KENNEDY T., KELLY M. J., and DOUGLAS G. J. (1972) Vagotomy for gastric ulcer. *Br. Med. J.* 2, 371–373.

KRAFT R. O., FRY W. J. and RANSON H. K. (1966) Vagotomy and pyloroplasty in the care of patients with gastric ulcer. *Arch. Surg.* 92, 456.

LOUW J. H. and MARKS I. N. (1977) The results of peptic ulcer surgery. *J. R. Coll. Surg. Edinb.* 22, 19–34.

[illegible]EIL A. D., [illegible]CADAM[illegible] and HUTCHINSON J. S F. (1969) Vagotomy and [illegible] in treatment of gastric ulcer. [illegible] *Surg. Gynecol. Ob*[illegible]8, 91–96.

[illegible]ILSEN J., AMDRUP E., [illegible]ISTIANSEN P. et al. (1973) Gastric ulcer II: surgical [illegible]ment. *Acta Chir. Scand.* 139, 460–465.

STEMMER E. A., ZAHN R. L., [illegible]HOM L. W. et al. (1968) Vagotomy and drainage [illegible]dures for gastric ulcer. *Arch. Surg.* 96, 586–591.

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Appendix

Statistical method

All results in this paper were analysed by compiling 2 × 2 contingency tables. The exact probability of each observed result was calculated using the following formula (Bailey, 1959).

a	b	$a+b$
c	d	$c+d$
$a+c$	$b+d$	n

$$P = \frac{(a+b)! \times (c+d)!\,(b+d)!\,(a\times c)!}{n!\,a!\,b!\,c!\,d!}$$

Results

Comparison of Visick grading between elective and emergency care:

	Poor (Visick 4+5)	Good or satisfactory (Visick 1+2+3)	
Elective operations	7	37	44
Emergency operations	2	8	10
	9	45	54

$P > 0{\cdot}32$.

Comparison of Visick grading between type I and type II+III ulcers having elective surgery:

	Poor	Good or satisfactory	
Type I ulcer	5	26	31
Type II+III ulcers	2	11	13
	7	37	44

$P > 0{\cdot}35$.

Comparison of Visick grading between those patients having an endoscopic examination and those not:

	Poor	Good or satisfactory	
No endoscopic examination	0	16	16
Endoscopic examination	3	25	28
	3	41	44

$P > 0{\cdot}25$.

Comparison of ulcer recurrence after elective operation for type I or type II+III ulcers.

	Recurrence	No recurrence	
Type I ulcer	3	28	31
Type II+III ulcers	1	12	13
	4	40	44

$P < 0{\cdot}43$.

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Lipid meta[illegible]nd nitrogen balance aft[illegible] abdominal [illegible] in man

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SUMMARY

The relation of lipid metabo[illegible] nitrogen balance was studied in patients having [illegible]rgo[illegible] abdominal surgery and was compared wit[illegible]rol [illegible]jects who [illegible]d fasted for a similar perio[illegible] [illegible]tie[illegible]s had lower [illegible]culating concentrations [illegible] glyc[illegible]ol, [illegible]on-esterified [illegible]ty acids and ketone bodies. T[illegible]ere were inverse [illegible]relations between blood alanine and ketone body [illegible]centrations in both patients ($r = -0{\cdot}64, P<0{\cdot}01$) [illegible] *controls* ($r = -0{\cdot}58, P<0{\cdot}01$). *Nitrogen excretion [illegible]tients (1[illegible] 7 mmol/kg body weight/day ± 1·4 s.e. was greater than by controls* ($9{\cdot}2$ mmol kg^{-1} [illegible] $0{\cdot}8, P<0{\cdot}05$), *but a more marked difference was [illegible]ed for urinary methyl histidine excretion of* $5{\cdot}1 \pm 0{\cdot}5$ [illegible] $kg^{-1} d^{-1}$ *by patients and only* $2{\cdot}5 \pm 0{\cdot}3$ µmol kg^{-1} [illegible]$^{-1}$ *by controls* ($P<0{\cdot}01$), *a disparity indicative of more active protein turnover after surgery.*

THE accelerated rate of nitrogen loss from the body after surgical operation or injury remains a matter of concern, especially when patients are unable to eat for protracted periods. Small amounts of glucose, about 0·55 mol (100 g) daily, can, however, decrease nitrogen loss in otherwise starving subjects (Gamble, 1946).

Infusion of ketone bodies into fasting obese subjects also causes a decrease in nitrogen excretion, and a decrease in blood alanine concentration in normal fasting subjects (Sherwin et al., 1975). Alanine has a key role in metabolism, being formed and released by muscle in quantities much exceeding its content in muscle and accounting for half the gluconeogenic substrate derived from amino acids (Felig, 1973). Blood ketone body concentrations increase remarkably during starvation in normal and obese subjects and become a predominant source of fuel. Gluconeogenesis from amino acids decreases after the first few days of starvation and this, with perhaps a direct inhibitory effect of ketones on muscle breakdown, may contribute to protein conservation (Cahill, 1976).

The absence of large increases in blood ketone body concentrations in certain seriously infected or injured patients suggests impaired ketogenesis, which may, with other metabolic and hormonal changes, contribute to the accelerated nitrogen loss (O'Donnell et al., 1976). Changes in levels of blood ketone bodies and other intermediary metabolites have not been fully investigated following surgical operations in completely starved patients. We have therefore compared the metabolic changes seen in patients after elective surgery with those observed in normal fasting volunteers.

Patients and methods

Six patients undergoing elective abdominal surgery were studied from the first to fourth postoperative day. None had significant endocrine, renal, hepatic or cardiorespiratory dysfunction, none was on concomitant drug therapy and none had postoperative complications. Anaesthesia was induced with intravenous thiopen[illegible]e and suxamethonium and maintained with halothane [illegible] nitrous oxide, tubocurarine being used as a muscle r[illegible]xant. Papaveratum and pr[illegible]xazine or metaclopramide were used in the early postoperative period to control pain or vomiting. From the start of the operation until 9 a.m. on day 1 patients received 2–3 l of 4·3 per cent (0·24 mol/l) glucose—0·18 per cent (0·03 mol/l) sodium chloride solution supplying 0·48–0·72 mol (86–129 g) glucose. Subsequently, they received 2–3 l/d 0·9 per cent (0·15 mol/l) saline with 27 mmol/l (2 g) potassium chloride. All patients were mobilized out of bed as much as possible from day 1.

Five healthy non-obese volunteers fasted for a similar period, that is from 10 p.m. the night before the equivalent to operation day (day 0). They took 0·27 mol (50 g) glucose orally at 9 p.m. on day 0 and at 7 a.m. on day 1. At other times they took only water by mouth and remained sedentary.

Estimations of ideal body weight were made (Metropolitan Life Insurance Co., 1959) and fat-free mass was assessed by measuring skinfold thicknesses (Durnin and Womersley, 1974) on each subject.

Fifteen-millilitre samples of free-flowing antecubital venous blood were taken after the subjects had rested supine for 1 h at 9 a.m. daily and at 9 p.m. on day 1. Blood, deproteinized immediately in 5 per cent (v/v) perchloric acid was centrifuged and the supernatant used for automated fluorimetric assay of glucose, alanine, lactate, glycerol and 3-hydroxybutyrate (Lloyd et al., 1978) and spectrophotometric assay of acetoacetate (Price et al., 1977). Plasma was used for assay of non-esterified fatty acids (NEFA) by a modification of the method of Ho and Meng (1969) and routine measurement of electrolytes. Serum insulin was measured by a double antibody method (Soeldner and Slone, 1965). Rapid centrifugation of 2·5 ml of blood taken into tubes containing 2500 i.u. aprotinin and 2·5 µmol Na EDTA gave plasma for assay of glucagon by a wick chromatography method (Ørskov et al., 1968). Serum cortisol was measured by a competitive protein binding technique (Kehlet et al., 1974).

Three consecutive 24-h urine collections were made from 9 a.m. on day 1 using 25 ml 5 N hydrochloric acid as preservative. Total urinary nitrogen excretion was measured by the micro-Kjeldahl technique and urinary 3-methylhistidine excretion was assessed with a Technicon TSM amino acid analyser using a lithium citrate buffer system.

Statistical comparisons were made using paired and unpaired Student's *t* tests.

Results

The fasting volunteers were younger than the surgical patients but in other respects the two groups were similar (*Table I*). Metabolite concentrations at 9 a.m. on days 0, 2 and 4 are shown in *Table II*. Before operation serum insulin was higher ($P<0{\cdot}05$) in the control subjects, but the concentrations of this and

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Table I: CHARACTER[illegible] OF PATIENTS STUDIED AFTER OPERATION [illegible] FASTING CONTROLS

Subject	Age (yr)	Sex	Body weight (kg)	Ideal body weight* (%)	Estimated fat-free weight† (kg)	[illegible]tion
Patients						
E. T.	73	F	72	126	52	Benign g[illegible] 1 partial gastrectomy
D. M.	41	M	75	109	62	Carcinom[illegible]; palliative partial gastrectomy
C. S.	53	M	85	109	68	Carcinoma o[illegible]m, palliative right hemicolectomy
I. Y.	71	F	48	92	34	Carcinoma o[illegible]; palliative left hemicolectomy
S. M.	60	F	52	86	39	Carcinoma [illegible]um; right hemicolectomy
P. M.	49	F	57	100	38	Duodenal [illegible] Polya gastrectomy
Mean±s.e. mean	58±5		65±10	104±6	49±6	
Fasting volunteers						
Mean±s.e. mean	27±3	2 M 3 F	68±7	109±4	53±6	

* Ideal body weight derived from the tables of Metropolitan Life Insurance Co. (1959).
† Estimated by the method of Durnin and Womersley (1974).

Table II: VENOUS BLOOD METABOLITE AND HORMONE CONCENTRATIONS IN FASTING SURGICAL PATIENTS AND CONTROLS (MEAN±S.E. MEAN)

	Preop. (day 0)		Day 2 postop.		Day 4 postop.	
	Volunteers ($n=5$)	Patients ($n=6$)	Volunteers ($n=5$)	Patients ($n=6$)	Volunteers ($n=5$)	Patients ($n=6$)
Glucose (mmol/l)	4·85±0 15	4·9±0·3	3·9±0 1	5·1±0 3**	3·3±0 2††	4 0±0 3†
Lactate (mmol/l)	0 66±0 08	0·60±0·06	0·69±0·05	0 65±0 04	0·71±0·07	0·65±0 05
Alanine (mmol/l)	0 30±0 03	0·37±0·05	0·22±0·01	0·18±0·02†	0·21±0.02	0·15±0 01*†
Glycerol (mmol/l)	0 054±0 010	0·053±0 009	0·104±0·008†	0 062±0 003**	0 125±0 20†	0·091±0 012†
NEFA (mmol/l)	0·32±0 08	0·33±0·08	0 86±0 15†	0 47±0·11	1 01±0·19†	0·73±0 22†
Ketone bodies (mmol/l)	0 11±0 05	0·06±0 01	2·25±0 35††	0·80±0·28**	5·68±0 12††	2 94±0·41**††
Insulin (mU/l)	8 0±0 8	5·7±0·8*	3·6±0·7†	4·7±0·7	3 4±1·5†	2 4±0 3†
Glucagon (ng/l)	60±11	69±7	101±14††	98±11†	105±18	68±15
Cortisol (mmol/l)	543±64	380±92	599±66	481±45	638±72	662±61†

Significance tests: patients *v.* volunteers, * $P<0·05$; ** $P<0·01$; postoperative level *v.* basal value, †$P<0·05$, †† $P<0·01$.

Table III: MEAN±S.E. MEAN URINE TOTAL NITROGEN AND 3-METHYLHISTIDINE EXCRETION IN THE FIRST 3 DAYS AFTER ABDOMINAL OPERATION IN 6 TOTALLY STARVED PATIENTS AND IN 5 HEALTHY VOLUNTEERS UNDERGOING A COMPARABLE PERIOD OF FASTING

	Patients	Fasting volunteers
Urine total nitrogen excretion (mmol kg^{-1} d^{-1})	12·7±1·4	9·2±0·8*
Urine 3-methylhistidine excretion (μmol kg^{-1} d^{-1})	5·1±0·5	2 5±0·3**

Significant difference between groups, * $P<0·05$, ** $P<0·01$.

other parameters were within the normal reference range after an overnight fast for this laboratory (Foster et al., 1978).

Glucose and alanine

Blood glucose concentration fell in both groups during the study, but was significantly higher in the surgical patients. Blood alanine concentration fell in both groups, insignificantly in the control subjects but in the patient group alanine concentration on day 4 was significantly less than before operation ($P<0·05$) and significantly less than in the fasting volunteers ($P<0·05$). There was a significant inverse correlation of alanine with ketone bodies in the patient ($r=-0·64$; $P<0·01$) and control groups ($r=-0·58$, $P<0·01$).

Lipid metabolites

There was a rise in all lipid metabolite concentrations in the fasting volunteers (*Table II*). In particular, ketone body (3-hydroxybutyrate plus acetoacetate) concentration in the volunteers rose to 5·68±0·12 mmol/l by day 4, but to only 2·94±0·41 mmol/l ($P<0·001$) in the patients. Within the patient group on day 4, ketone body concentrations were generally highest in the eldest patients. On day 4 the youngest patient (male, 41 years) had a blood ketone body concentration of 1·90 mmol/l compared with 5·86 mmol/l in the oldest control (male, 35 years).

Hormones

During the period of complete fasting, serum immunoreactive insulin concentration fell to low and similar values in each group. Plasma glucagon rose significantly in both groups but remained elevated on day 4 only in the control group. There was a significant rise in serum cortisol concentration after operation and at 9 p.m. on day 1 serum cortisol in patients (523±111 nmol/l) was higher than in the fasting volunteers (231±35 nmol/l, $P<0·05$).

Electrolytes

There were no changes in the plasma sodium or potassium concentration in either group but plasma bicarbonate fell during the study from 27±1 mmol/l to 20±1 mmol/l in the volunteers ($P<0·01$) and from 26±1 mmol/l to 22±1 mmol/l in the patients ($P<0·01$). The volunteers had a mean urinary sodium loss of 71 mmol/d whereas the patients whose mean intake was 269 mmol/d had a positive balance of 125 mmol/d, exclusive of cutaneous losses. Mean urinary potassium loss by the volunteers was 34 mmol/d whereas patients who received a mean of 48 mmol potassium/d had a net loss of 22 mmol/d.

Nitrogen excretion (*Table III*)

Mean urinary nitrogen excretion in the 3-day study period was 9·2 mmol kg^{-1} d^{-1} by the volunteers and 12·7 mmol kg^{-1} d^{-1} by the patients ($P<0·05$). The mean urinary 3-methylhistidine excretion by control subjects was 2·5 μmol kg^{-1} d^{-1}, also lower than that by the patients (5·1 μmol kg^{-1} d^{-1}, $P<0·01$). No significant correlations between lipid metabolites or hormones and nitrogen excretions were observed except for plasma glucagon and urine nitrogen in patients ($r = 0·71$, $P<0·01$) and controls ($r = 0·54$, $P<0·05$).

Discussion

Starvation is known to result in a fall in blood glucose and insulin and a rise in lipid metabolites (Cahill et al., 1966). Similarly, blood alanine concentrations fall (Felig et al., 1969) and glucagon rises in the early phases of starvation (Aguilar Parada et al., 1969). These changes were observed in both our fasted controls and postoperative patients, but the extent of these physiological changes was smaller in the surgical patients. As expected, blood glucose and nitrogen excretion increased after operation. In association with lower blood alanine concentrations after operation, this implies increased hepatic extraction of alanine for gluconeogenesis and ureagenesis in the early postoperative period. This may account for the correlation of glucagon with urine nitrogen since glucagon appears to have little effect on protein metabolism outside the liver (Fitzpatrick et al., 1977). The similarity in serum insulin in the two groups, despite higher blood glucose concentration after operation, suggests inhibition of secretion of insulin, perhaps similar to that noted in the peroperative period (Allison et al., 1967).

The mean nitrogen excretion can be calculated to be equivalent to a loss of 170 g amino acid by a 70-kg control subject in the 3-day study period and of 235 g amino acid by a 70-kg patient, an excess of 65 g after operation. 3-Methylhistidine is an amino acid which is found in particularly high concentration in muscle and which is excreted unchanged and not reincorporated into muscle after breakdown (Long et al., 1975). Its excretion is thus a useful marker of muscle protein turnover, which probably accounts for half of total body protein turnover (Long et al., 1977). Assuming a content of 3-methylhistidine in human muscle of 1·76 mol/g dry weight (Asatoor and Armstrong, 1967), approximately 300 g dry muscle protein was broken down by the controls in the 3-day study period and 600 g by the patients. The disparity between these losses and that calculated from nitrogen excretion indicates considerable protein synthesis from amino acids released from muscle by both groups, but particularly by the postoperative patients. Previous workers have noted increased 3-methylhistidine excretion in some severely injured subjects (Williamson et al., 1977).

Studies on protein turnover after surgery using isotopically labelled amino acids showed similar rates of breakdown in controls and patients but slightly depressed rates of protein synthesis postoperatively (O'Keefe et al., 1974; Crane et al., 1977). Such isotope studies consider whole body turnover just as urinary nitrogen represents whole body net protein breakdown, but the disparity with our results is surprising.

Our patients were found to have depressed circulating concentrations of NEFA and particularly of ketone bodies, with inverse correlations between blood ketone bodies and alanine in both groups. *In vitro* ketone bodies have been observed to decrease alanine release from isolated muscle (Palaiologis and Felig, 1976). The lower ketone body concentration in the patient may in part account for the observed increase in muscle protein breakdown. However, blood alanine concentration fell more quickly in the patients, which also implies both a change in the normal ketone body/alanine relationship and increased hepatic amino acid extraction.

Glycerol is released by adipose tissue on hydrolysis of triglyceride and is taken up by the liver at a rate dependent upon its concentration (Shaw et al., 1976). The lower glycerol concentrations in the patients suggest that lipolysis was stimulated less after operation than during simple starvation. The metabolic rate is known to change little after operation (Kinney, 1967) and therefore the depressed ketone body levels are probably due to decreased production rather than increased extraction. Ketone body production is in part related to NEFA concentration (McGarry and Foster, 1972). Both lipolysis and ketogenesis are well known to be very readily inhibited by small concentrations of insulin, which is probably the main regulatory mechanism for these processes. Serum insulin concentrations were similar in both groups and the relative impairment in lipolysis and ketogenesis postoperatively is unexplained. Glucagon has ketogenic properties, but these are relatively weak and ineffective in the presence of even low concentrations of insulin (Schade and Eaton, 1975). Our findings on lipid metabolism are surprising since cortisol (for which we noted both a rise in concentration and a loss of diurnal variation after operation) and particularly catecholamines (for which rises in concentration during and after operation have previously been described [Nikki et al., 1972]) have lipolytic actions. Nevertheless, a comparable finding of an inverse relationship of ketone body concentration after orthopaedic injury to the severity of injury despite similar insulin concentrations in the more and less severely injured, has already been reported (Williamson and Smith, 1979).

It is likely that the differences noted between patients and controls were the result of operation itself. Halothane anaesthesia causes little metabolic disturbance (Oyama and Takazawa, 1971) and postoperative medication was not required in the latter part of the study. As expected, the patients were in positive sodium balance, whereas, again as expected, the control subjects were in negative sodium balance (Boulter et al., 1974). It seems unlikely that these factors could account for the marked differences noted. The patients received a small amount of glucose intravenously before the test period, and the controls a similar amount orally. The route of administration of glucose does not alter its effect on nitrogen balance (Fitzpatrick et al., 1975) and would appear unlikely to affect metabolic parameters 24–72 h later. The patients were older, but this is unlikely to have caused the observed differences. After an overnight fast blood ketones and NEFA concentrations are higher in older subjects (Foster et al., 1978) and during the study ketone body concentrations tended to rise more in the older patients. Nitrogen turnover is decreased in the elderly (Golden and Waterlow, 1977) so that the differences in ketone body and nitrogen metabolism we observed [illegible] have been more marked had we had controls of similar age to the patients.

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References

AGUILAR PARADA E., EISENTRAUT A. and UNGER R. (1969) Effects of starvation on plasma pancreatic glucagon in man. *Diabetes* **18**, 717–723.

ALLISON S. P., PROWSE K. and CHAMBERLAIN M. J. (1967) Failure of insulin response to glucose load during operation and after myocardial infarction. *Lancet* **1**, 478–480.

ASATOOR A. M. and ARMSTRONG M. D. (1967) 3-Methylhistidine—a component of actin. *Biochem. Biophys. Res. Commun.* **26**, 168–174.

BOULTER P. R., SPARK R. F. and ARKY R. A. (1974) Dissociation of the renin–aldosterone system and refractoriness of the sodium retaining action of mineralocorticoid during starvation in man. *J. Clin. Endocrinol. Metabol.* **38**, 248–254.

CAHILL G. F. (1976) Regulation of protein and amino acid metabolism. *Circ. Res.* **38**, Suppl. pp. 109–114.

CAHILL G. F., HERRERA M. G., MORGAN A. P. et al. (1966) Hormone fuel interrelationships during fasting. *J. Clin. Invest.* **45**, 1751–1769.

CRANE C., PICOU D., SMITH R. et al. (1977) Protein turnover in patients before and after elective orthopaedic operations. *Br. J. Surg.* **64**, 129–133.

DURNIN J. and WOMERSLEY J. (1974) Body fat assessed from total body density and its estimation from skinfold thicknesses. Measurements on 481 men and women aged 16–72 years. *Br. J. Nutr.* **32**, 77–99.

FELIG P. (1973) The glucose–alanine cycle. *Metabolism* **22**, 179–207.

FELIG P., OWEN O., WAHREN J. et al. (1969) Amino acid metabolism during prolonged starvation. *J. Clin. Invest.* **48**, 584–594.

FITZPATRICK G., MEGUID M., GITLITZ P. et al. (1977) Glucagon infusion in normal man. Effects on 3-methylhistidine excretion and plasma amino acids. *Metabolism* **26**, 477–485.

FITZPATRICK G., MEGUID M., O'CONNEL R. et al. (1975) Nitrogen sparing by carbohydrate in man. Intermittent or continuous enteral compared with continuous parenteral glucose. *Surgery* **78**, 105–113.

FOSTER K. J., ALBERTI K. G. M. M., HINKS L. et al. (1978) Blood intermediary metabolite and insulin concentration after an overnight fast. Reference ranges and interrelations. *Clin. Chem.* **24**, 1568–1572.

GAMBLE J. L. (1946) Physiological information gained from studies on the life raft ration. *Harvey Lecture 42*, pp. 247.

GOLDEN M. and WATERLOW J. (1977) Total protein synthesis in elderly people: a comparison of results with ^{15}N glycine and ^{14}C leucine. *Clin. Sci. Mol. Med.* **53**, 227–288.

HO R. J. and MENG H. C. (1969) A simple and ultrasensitive method for determination of free fatty acids by radiochemical assay. *Analyt. Biochem.* **31**, 426–436.

KEHLET H., BINDER C. and ENGBAEK C. (1974) Cortisol binding capacity in plasma during anaesthesia and surgery. *Acta. Endocrinol.* **75**, 119–124.

KINNEY. J. M. (1967) The effect of injury on metabolism. *Br. J. Surg.* **54**, 435–437.

LEE H. A. (1977) *Parenteral Nutrition in Acute Metabolic Illness.* London, Academic Press, p. 315.

LLOYD B., BURRIN J., SMYTHE P. et al. (1978) Simple automated enzymatic fluorimetric assay for blood glucose, lactate, pyruvate, alanine, glycerol and 3-hydroxybutyrate. *Clin. Chem.* **24**, 1724–1729.

LONG C. L., HAVERBERG L. N., YOUNG V. R. et al. (1975) Metabolism of 3-methylhistidine in man. *Metabolism* **24**, 929–935.

LONG C. L., SCHILLER W., BLACKMORE W. et al. (1977) Muscle protein catabolism in the septic patients as measured by 3-methylhistidine excretion. *Am. J. Clin. Nutr.* **30**, 1349–1352.

MCGARRY J. D. and FOSTER D. W. (1972) Regulation of ketogenesis and clinical aspects of the ketotic state. *Metabolism* **21**, 471–489.

NIKKI P., TAKKI S., TAMMISTO T. et al. (1972) Effect of operative stress on plasma catecholamine levels. *Ann. Clin. Res.* **4**,146–151.

O'DONNELL T., CLOWES G., BLACKBURN G. et al. (1976) Proteolysis associated with a deficit of peripheral energy fuel substrates in septic man. *Surgery* **80**, 192–200.

O'KEEFE S. J., SENDER P. M. and JAMES W. P. (1974) Catabolic loss of body nitrogen in response to surgery. *Lancet* **2**, 1035–1037.

ØRSKOV H., THOMSON H. G. and YDE H. (1968) Wick chromatography for rapid and reliable immunoassay of insulin, glucagon and growth hormone. *Nature (Lond.)* **219**, 193–195.

OYAMA T. and TAKAZAWA T. (1971) Effects of halothane anaesthesia and surgery on human growth hormone and insulin levels in plasma. *Br. J. Anaesth.* **43**, 573–580.

PALAIOLOGIS G. and FELIG P. (1976) Effects of ketone bodies on amino acid metabolism in isolated rat diaphragm. *Biochem. J.* **154**, 709–716.

PRICE C. P., LLOYD B. and ALBERTI K. G. M. M. (1977) A kinetic, spectrophotometric assay for rapid determination of acetoacetate in blood. *Clin. Chem.* **23**, 1893–1897.

SCHADE D. and EATON R. P. (1975) Modulation of fatty acid metabolism by glucagon in man. *Diabetes* **24**, 502–515.

SHAW W., ISSEKUTZ T. and ISSEKUTZ B. (1976) Gluconeogenesis from glycerol at rest and during exercise in normal, diabetic and methyl-prednisone treated dogs. *Metabolism* **25**, 329–339.

SHERWIN R., HENDLER R. and FELIG P. (1975) Effect of ketone infusions on amino acid and nitrogen metabolism in man. *J. Clin. Invest.* **55**, 1382–1390.

SOELDNER J. and SLONE D. (1965) Critical variables in radioimmunoassay of serum insulin using the double antibody technique. *Diabetes* **14**, 771–779.

WILLIAMSON D. H., FARRELL R., KERR A. et al. (1977) Muscle protein catabolism in man as measured by urinary excretion of 3-methylhistidine. *Clin. Sci. Mol. Med.* **52**, 527–533.

WILLIAMSON D. H. and SMITH R. (1979) Ketone bodies and injury in man. In: KARRAN S. and ALBERTI K. G. M. M. (ed.) *Practical Nutritional Support.* Tunbridge Wells, Pitman. (In the press.)

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Comparison of brush cytology before or a[illegible] biopsy for diagnosis of gastric carcinoma*

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SUMMARY

A randomized trial has compared the res[illegible] of brush cytology before or after biopsy in patients [illegible] solitary gastric lesions. One hundred and eleven carcinomas were identified in 324 patients. False positive histological reports were recorded in 2 patients but there were no false positive cytology results. The cumulative accuracy of biopsy and cytology in patients with carcinoma was 97 per cent, which was significantly better than biopsy a[illegible] (83 per cent, $P<0{\cdot}001$) or cytology alone (87 per cent, $P<0{\cdot}001$). The cumulative results of brushing before biopsy were significantly better than results obtained by brushing after biopsy ($P<0{\cdot}05$) and indicate that brush cytology should normally be performed before biopsy.

THERE is a wide variation in the reported accuracy of endoscopic biopsy (Kobayashi et al., 1970) and brush cytology (Hermanek, 1973) in the diagnosis of gastric carcinoma. The benefit of obtaining both cytological and histological material has already been emphasized (Witzel et al., 1976). Although most investigators prefer to brush before biopsy, it has been suggested that if gastric lesions are brushed first, the accuracy of subsequent biopsy may be reduced (Smithies et al., 1975). To investigate this hypothesis we have undertaken a prospective randomized trial of brush cytology before or after biopsy amongst patients with solitary gastric lesions attending for elective endoscopy.

Patients and methods

Patients with solitary gastric lesions seen on elective upper gastrointestinal endoscopy at the General Hospital or Queen Elizabeth Hospital, Birmingham, between January 1975 and October 1977, entered the trial. Only patients who had a barium meal before endoscopy were admitted for study. Instructions on numbered randomization cards indicated whether the lesion should be brushed before or after biopsy. Of the 347 patients who were included in the study, 23 were withdrawn either because they had had a previous endoscopy and had therefore been entered twice or because of failure to attend for clinical or endoscopic review.

Endoscopy was performed by four clinicians using the Olympus GIFD or GIFK endoscope. At least four biopsies were obtained using the ACM (American Cystoscope Manufacturers) Martin biopsy forceps with a bayonet needle (catalogue number 70354). Material was collected for cytology by vigorous brushing of the lesion with a non-disposable nylon brush. Cases of carcinoma were excluded unless the diagnosis had been confirmed by operation, repeat endoscopy or autopsy. Patients with benign disease were excluded unless they attended for a repeat endoscopy (usually 6 weeks) or were reviewed at follow-up for at least 6 months or until symptom-free.

The histological material was examined in the pathology department by any member of the university staff, whereas the cytological smears were reported by one person (H. T.). The material obtained by gastric brushing was smeared on to a glass slide and fixed immediately in alcohol. The smear was stained using the Papanicolaou technique. Of the patients who completed the trial, brushing was performed before biopsy in 161 patients and after biopsy in 163 patients.

Table I: OVERALL RESULTS

	Carcinoma ($n=111$)	Non-malignant ($n=213$)
Positive histology alone	92 (83%)	2 (1%)
Positive cytology alone	96 (87%)	0
One or other technique, positive	106 (97%)***	2 (1%)

*** $P<0{\cdot}001$ compared with histology alone or cytology alone.

Table II: RESULTS OF THE TRIAL

	Positive histology	Positive cytology	One or other technique positive
Brush before			
Carcinoma ($n=57$)	47 (82%)	52 (91%)	57 (100%)
Non-malignant ($n=104$)	0	0	0
Total errors	10	5	0
Brush after			
Carcinoma ($n=54$)	45 (83%)	44 (82%)	49* (91%)
Non-malignant ($n=109$)	2	0	2
Total errors	11	10	7**

* $P<0{\cdot}05$ compared with cumulative accuracy of brush cytology before biopsy.
** $P<0{\cdot}01$ compared with total number of errors using brush cytology before biopsy.

Results

A final diagnosis of carcinoma was recorded in 111 patients. In 15 cases the tumour involved the oesophagus but only 5 were squamous cell lesions. There were 2 patients with early gastric carcinoma.

The accuracy of biopsy in patients with gastric carcinoma (83 per cent) was inferior to the accuracy of cytology alone (87 per cent); however, this difference was not statistically significant (*Table I*). When the cumulative accuracy of a positive pathological diagnosis from one or other technique was calculated (97 per cent) this was found to be significantly better than either cytology alone ($\chi^2 = 12{\cdot}3$, $P<0{\cdot}001$) or histology alone ($\chi^2 = 10{\cdot}0$, $P<0{\cdot}001$). There were two false positive histology reports. Both were in patients with gastric ulcer who subsequently underwent gastrectomy and the final diagnosis in the resected specimen indicated that both lesions were benign. By contrast, there were no false positive cytological findings.

The results of the trial (*Table II*) have indicated that the cumulative accuracy of cancer diagnosis was significantly better when brush cytology was performed before biopsy (100 per cent) as compared with the results of brushing after biopsy (91 per cent) ($\chi^2 = 5{\cdot}3$,

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* This work was presented in part at the Surgical Research Society in January 1979.

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$P<0{\cdot}05$). This difference was due to a reduction in the accuracy of brush cytology from 91 per cent when the lesion was brushed first and only 82 per cent when brushing was performed after biopsy. The total number of errors was significantly less when brushing was performed first ($P<0{\cdot}01$).

Discussion

The results of this trial indicate that, provided an experienced cytological service is available, brush cytology should always be performed as well as biopsy. The cumulative results were significantly better than either procedure taken in isolation. Our cumulative accuracy was as good as the results obtained from multiple biopsies, a technique which is extremely time-consuming for the endoscopist as well as for the histopathology department (Dekker and Tytgat, 1977). Using both criteria, only 5 patients with cancer were missed at the first endoscopic examination. One of these patients was lost to follow-up and returned with a haematemesis 6 months later. All other patients were thought to have a carcinoma from the macroscopic appearance of the tumour and the repeat endoscopic examination confirmed the lesion to be malignant. None of the other patients with non-malignant biopsies or brush cytology had clinical or endoscopic evidence of gastric carcinoma during follow-up.

The accuracy of biopsy diagnosis in this study is not as good as in most other reports, the average value for an accurate histological diagnosis being 87 per cent (Hermanek, 1973). However, our biopsies were reported by all members of the histopathology department. Although all the biopsy specimens were later reviewed by one person, it was felt that the results of this study should be analysed according to the initial reports. When the histology was reviewed, both false positives were considered to be non-malignant but only one of the false negative reports was changed. The results of the initial reports indicate normal hospital practice rather than the artificial situation of a single person's interpretation of the biopsies, which never reflects the accuracy outside a clinical trial (Segal et al., 1975). By contrast, cytological material from both the hospitals in this study is always reported by one person and we felt that there was no justification for changing this practice during the trial. It is encouraging that we were able to record no false positive cytological reports, which is in marked contrast to the experience of other units (Sherlock et al., 1972; Weidenhiller, 1974).

Our results have also shown that brushing does not impair the accuracy of subsequent biopsy since the accuracy of histology in both groups was the same. However, the accuracy of brush cytology was less reliable when biopsies had been performed first, indicating that biopsy may make interpretation of brush cytology difficult. Furthermore, it is often difficult to localize the site of malignancy if biopsy has caused bleeding. When brushing was performed before biopsy there were no false positive results and the diagnosis of carcinoma was never missed using both diagnostic methods. When brushing was performed after biopsy there were 2 false positive reports and 5 cases of carcinoma were missed by both methods (7 errors). This difference is statistically significant and indicates that brush cytology should normally be performed before biopsy.

Acknowledgements

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References

DEKKER W. and TYTGAT G. N. (1977) Diagnostic accuracy of fibre-endoscopy in the detection of upper intestinal malignancy: a follow-up analysis. *Gastroenterology* 73, 710–714.

HERMANEK P. (1973) Gastrobiopsy in cancer of the stomach. *Endoscopy* 5, 144–147.

KOBAYASHI S., PROLLA J. C. and KIRSNER J. B. (1970) Brushing cytology of the oesophagus and stomach under direct vision fibrescopes. *Acta Cytologica* 14, 219–223.

SEGAL A. W., HEALY M. J. R., COX A. G. et al. (1975) Diagnosis of gastric cancer. *Br. Med. J.* 2, 669–672.

SHERLOCK P., EHRLICH A. N. and WINAWER S. J. (1972) Diagnosis of gastrointestinal cancer—current status and recent progress. *Gastroenterology* 63, 672–700.

SMITHIES A., LOVELL D., HISHORN S. et al. (1975) The value of brush cytology in the diagnosis of gastric cancer. *Gut* 16, 395.

WEIDENHILLER S. (1974) Gastroenterologische Zytodiagnostik. *Dtsch. Med. Wochenschr.* 99, 8–11.

WITZEL L., HALTER F., GRETILLAT P. A. et al. (1976) Evaluation of specific value of endoscopic biopsies and brush cytology for malignancies of the oesophagus and stomach. *Gut* 17, 375–377.

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Spontaneous an[illegible]natic rupture of hepatoma

NAOFUMI NAGASUE AN[illegible]HI INOKUCHI*

SUMMARY

Hepatoma is a common cause of spontaneous rupture of the liver. During recent years, spontaneous rupture was found in 11 (7 per cent) of 157 patients with hepatoma. The rupture occurred spontaneously in [illegible] patients, traumatically in 1 while in 3 patients trivial trauma seemed to be the precipitating factor. A correct preoperative diagnosis was made in 7 patients, all of whom were known to have a hepatoma. Hepatic resection was performed in 4 patients, 2 of whom were long-term survivors. Haemorrhage stopped in 2 of 3 patients who underwent hepatic artery ligation, but only 1 patient was discharged from hospital. The remaining patients, who were treated by packing, suture or laparotomy alone, died within a short time after admission. It is suggested that resection is the preferred management, but if this is not possible hepatic artery ligation should be performed.

PRIMARY carcinoma of the liver is a challenging disease, because it is difficult to diagnose and may present management problems. One such problem is rupture of the carcinoma with intraperitoneal bleeding. This complication is rare in Caucasians (MacDonald, 1957; El-Domeiri et al., 1971; Kew et al., 1971), but is more frequent among Chinese (Ong et al., 1965; Kuo et al., 1970) and South Africans (Alpert et al., 1969). In the English literature there are many case reports (Hermann and David, 1973; Okezie and DeAngelis, 1974; Arnersjo et al., 1975; Mokka et al., 1976), but few series have been reported. The management of 11 such patients is presented and the preferred treatment for this condition discussed.

Patients and methods

Between January 1967 and May 1978, 124 patients with a hepatoma were admitted to the Second Department of Surgery, Kyushu University. Six presented as spontaneous ruptures and 1 as a traumatic rupture. Between 1969 and 1974, 33 patients with hepatoma were seen at the Department of Surgery, Saiseikai Yahata Hospital, Kitakyushu. Spontaneous rupture occurred in 4 patients. Of this series of 11 patients, 9 were male and 2 female. The average age was 54 years (range 43–69 years).

The mode of presentation is summarized in *Table I*. All the patients experienced abdominal pain of mild to severe degree; the pain was sudden in onset in 8 patients but started gradually in the remaining patients. Four patients were admitted in haemorrhagic shock while 3 patients never experienced a blood pressure lower than 90 mmHg. A diagnostic paracentesis was carried out in 7 patients, and blood was aspirated in 6. Five patients had a history of liver disease: cirrhosis in 2 patients, chronic hepatitis in another 2 and schistosomiasis in 1. A correct diagnosis was made in all 7 patients who were known to have a hepatoma, but the condition was not diagnosed until laparotomy or post-mortem examination in the remaining 4 patients. The overall incidence of spontaneous rupture in 157 patients was 7 per cent.

Serum alpha-fetoprotein level was determined in 8 patients; it was elevated in 5. Hepatitis B antigen was estimated in 9 cases, and 5 showed a positive reaction.

The macroscopic appearances are summarized in *Table II*. Associated cirrhosis was present in 9 patients and fibrosis in 1 patient.

Hepatic resection was performed in 4 patients, haemostasis being achieved in all. Two of these patients died of hepatic failure 3 and 30 days after operation. The third patient lived for 2½ years, but finally died of recurrence of the tumour. One patient is alive 10 months after operation without any recurrence. Hepatic artery ligation was carried out in 3 patients and the haemorrhage was stopped in 2 of them. Only 1 of these patients lived for more than 3 months. The remaining patients who underwent packing, suture, laparotomy alone or no treatment all died within a short period following admission.

Discussion

Hepatoma is the major cause of spontaneous rupture of the liver. Recently, the rupture of hepatic adenoma by oral contraceptives has been reported in the USA (Catalano et al., 1977), but this is very rare in Japan where the contraceptive pill is prohibited. MacDonald (1957) found 4 cases of spontaneous rupture among 84 patients with hepatoma in Boston City Hospital, while El-Domeiri et al. (1971), who reported 137 cases of hepatoma from New York, did not describe a patient with spontaneous rupture. In London, only 2 cases were found in 75 hepatoma patients (Kew et al., 1971). Acute haemoperitoneum occurred in 15 per cent of Ugandan patients (Alpert et al., 1969) and in Taiwan spontaneous rupture occurred in 13 per cent of 93 patients with hepatoma (Kuo et al., 1970). A similar figure, 12·8 per cent, was reported in Hong Kong (Ong et al., 1965). The cause of rupture may be related to minor trauma; in this series 2 patients had a spontaneous rupture following medical examination and a third during a journey in an ambulance.

In the absence of a known hepatoma, diagnosis is difficult. The presence of the clinical signs of liver disease such as spider naevi, palmar erythema, gynaecomastia or jaundice should suggest the diagnosis. A paracentesis is valuable, showing a haemoperitoneum in 6 of 7 patients in this series. Emergency arteriography may locate the tumour and the bleeding vessel, although arteriography failed in 1 patient (*Case* 2) to identify the hepatoma or the site of haemorrhage.

The ideal treatment of a ruptured hepatoma is hepatic resection, and satisfactory results have been obtained by this treatment (Hermann and David, 1973; Arnersjo et al., 1975; Mokka et al., 1976).

Unfortunately, many patients with hepatoma have cirrhosis, and these patients withstand haemorrhage and hepatic resection poorly, 2 of our patients undergoing resections dying with hepatic failure during the immediate postoperative period. In patients whose liver function is impaired by cirrhosis or who have multiple tumours, resection will not prove satisfactory. For this group hepatic artery ligation is an alternative, being successful in 2 of the 3 cases in this series. In addition, ligation with or without portal vein ligation may induce tumour regression (Nagasue et al., 1976). Packing or suture of the rupture should be avoided;

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Table I: PREOPERATIVE CLINICAL DETAILS OF 11 PATIENTS

Patient no.	Sex/age (yr)	Pain	Shock	Para-centesis	Hist[illegible] liv[illegible]	[illegible]ce and cause of rupture	Preoperative diagnosis
1	F/69	Sudden, mild epigastric	Yes	Positive	Chr[illegible] h[illegible]	In hospital, palpation?	Rupture of hepatoma
2	M/60	Sudden, severe RUQ, back	Yes	Negative	No	At home, spontaneous	Retroperitone[illegible] haemorrhag[illegible]
3	M/49	Sudden, moderate epigastric	Yes	np	Liv[illegible]s	At home, after bathing	Perforated [illegible]
4	F/58	Sudden, moderate epigastric	Yes	np	Live[illegible]osis	In hospital, spontaneous	Rupture of hepatom[illegible]
5	M/45	Sudden, severe epigastric	Yes	Pos[illegible]	No	In hospital, spontaneous	Rup[illegible] hepato[illegible]
6	M/55	Gradual, mild generalized	Yes	np	Sc[illegible]omiasis [illegible]ca	In hospital, by ambulance?	Rupture [illegible] hepatom[illegible]
7	M/43	Sudden, moderate upper abdomen	Yes	Positive	No	At ground, traumatic	Rupture of [illegible]er
8	M/51	Sudden, moderate epigastric	No	Positive	No	In hospital, palpation	Rupture of hepatoma
9	M/48	Gradual, mild generalized	No	Positive	No	In hospital, spontaneous	Rupture of hepatoma
10	M/56	Sudden, moderate RUQ	Yes	np	No	Outside while fishing	Perforated ulcer
11	M/62	Gradual, moderate RUQ	No	Positive	Chronic hepatitis	In hospital, spontaneous	Rupture of hepatoma

RUQ, right upper quadrant; np, not performed.

Table II: HISTOPATHOLOGIC FINDINGS, TREATMENT AND RESULTS OF 11 PATIENTS

Patient no.	Macro-scopic type* of tumour	Histology of tumours† Type	Edmondson	Liver cirrhosis	Treatments	Results and cause of death
1	Massive	Trabecular	II	Portal	Left lobectomy	Died, 3 d Hepatic failure
2	Nodular	Tubular	II	Portal	HAL+packing	Died, 1 d Haemorrhage
3	Nodular	Trabecular	III	Post-necrotic	Left lateral segmentectomy	Died, 2·5 yr Recurrence
4	Massive			Yes, but type unknown	Suture	Died, 19 d GI bleeding
5	Massive	Trabecular	III	Fibrosis	HAL	Died, 16 d Uraemia
6	Massive	Trabecular	III	Portal	Conservative	Died, 1 d Haemorrhage
7	Nodular	Trabecular	III	Portal, schistosomiasis japonica	Partial hepatectomy	Living, 10 mth
8	Massive	Trabecular	III	No	HAL	Died, 102 d Cachexia
9	Nodular	Trabecular	II	Post-necrotic	Exploratory laparotomy	Died, 15 d GI bleeding
10	Nodular	Undifferen-tiated	IV	Post-necrotic	Packing and suture	Died, 6 d Hepatic failure
11	Massive	Trabecular	III	Portal	Extended right lobectomy	Died, 30 d Hepatic failure

* Eggel (1901). † Edmondson et al. (1954). HAL, Hepatic artery ligation; GI, gastrointestinal.

all patients who had this treatment died within a short period of the operation.

The prognosis of spontaneous rupture of a hepatoma is poor. The outcome depends on the degree of coexistent cirrhosis, the position of the tumour or tumours and the general condition of the patient. Resection undoubtedly offers the better long term results, but hepatic artery ligation is worth considering as a short term management, either because of inexperience of the surgeon with hepatic resection or because the tumour is not resectable.

References

ALPERT M. E., HUTT M. S. R. and DAVIDSON C. S. (1969) Primary hepatoma in Uganda: a prospective clinical and epidemiologic study of forty-six patients. *Am. J. Med.* 46, 794–802.

ARNERSJO B., BENGMARK S., IHSE I. et al. (1975) Spontaneous rupture of the liver. *Acta Chir. Scand.* 141, 399–402.

CATALANO P. W., EARLY M. E., TOPOLOSKY H. W. et al. (1977) Focal nodular hyperplasia of the liver: a report of six patients. *Cancer* 39, 587–591.

EDMONDSON H. A. and STEINER P. E. (1954) Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer* 7, 462–503.

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EGGE[redacted] Über das primare Carcinom der Leber. *Beitr. Path. Anat. Allg. Pathol.* 30, [illegible]–604.

EL-DOMEIRI A. A., HUVOS A. G., GOLDSMITH H. S. et al. (1971) Primary malignant tumor of the liver. *Cancer* 27, 7–11.

HERMANN R. E. and DAVID T. E. (1973) Spontaneous rupture of the liver caused by hepatomas. *Surgery* 74, 715–719.

KEW M. C., DOS SANTOS H. A. and SHERLOCK S. (1971) Diagnosis of primary cancer of the liver. *Br. Med. J.* 4, 408–411.

KUO T. P., YANG Z. T. and LIN W. L. (1970) Twelve cases of rupture of hepatoma. *J. Formosan Med. Assoc.* 69, 425–436.

MACDONALD R. A. (1957) Primary carcinoma of the liver: a clinicopathologic study of one hundred and eight cases. *Arch. Intern. Med.* 99, 266–279.

MOKKA R., SEPPALA A., HUTTUNEN R. et al. (1976) Spontaneous rupture of liver tumors. *Br. J. Surg.* 63, 715–717.

NAGASUE N., INOKUCHI K., KOBAYASHI [illegible] et al. (1976) Hepatic dearterialization for nonresectable primary and secondary tumors of the liver. *Cancer* 38, 2593–2603.

OKEZIE O. and DEANGELIS G. (1974) Spontaneous rupture of hepatoma: a misdiagnosed surgical emergency. *Ann. Surg.* 179, 133–135.

ONG G. B., CHU E. P. H., YU F. Y. K. et al. (1965) Spontaneous rupture of hepatocellular carcinoma. *Br. J. Surg.* 52, 123–129.

Paper accepted 14 October 1978.

On having a paper rejected

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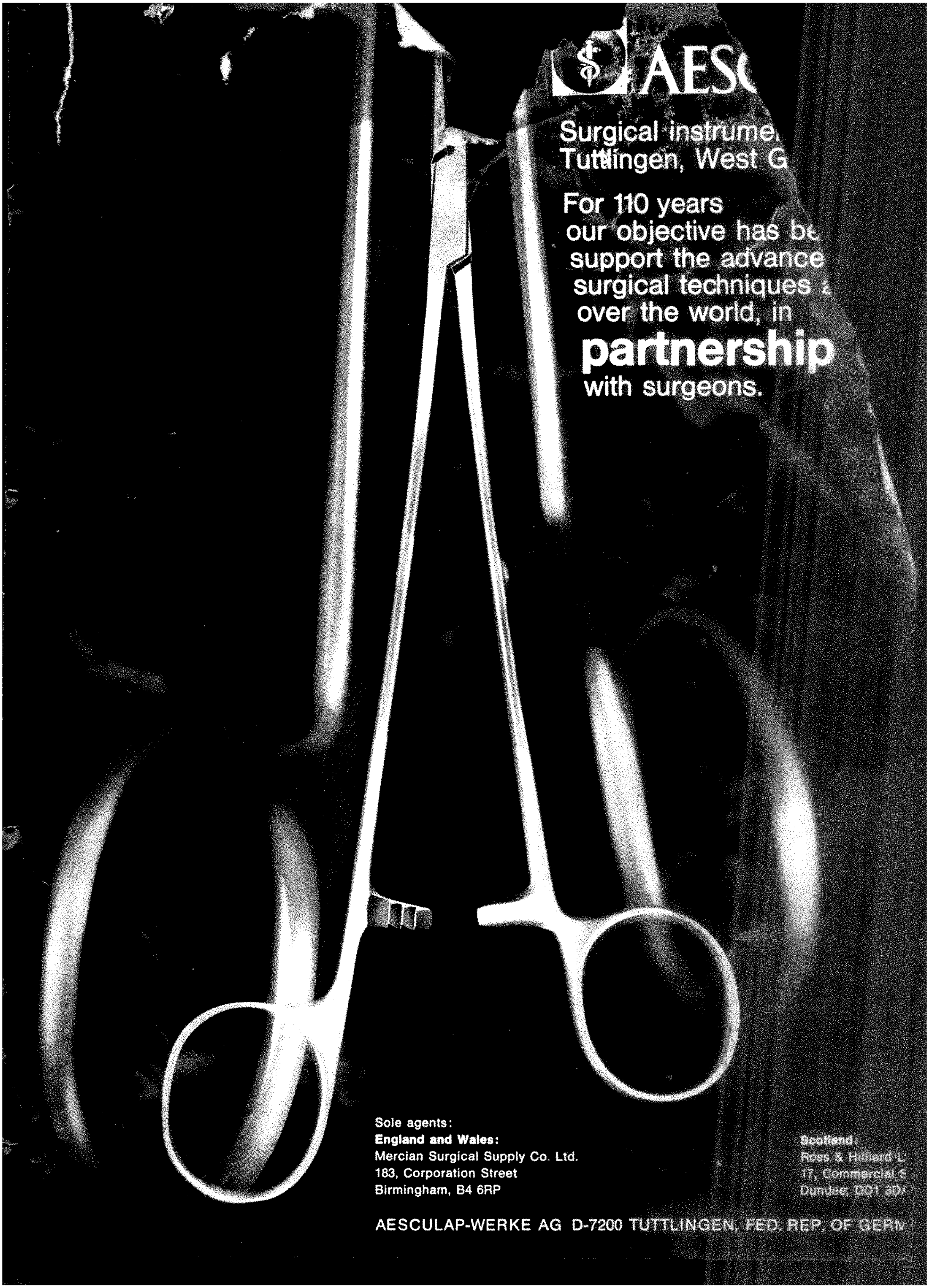
WATSON J. (1978) Making history pay. *The Author* 39, 189–192.



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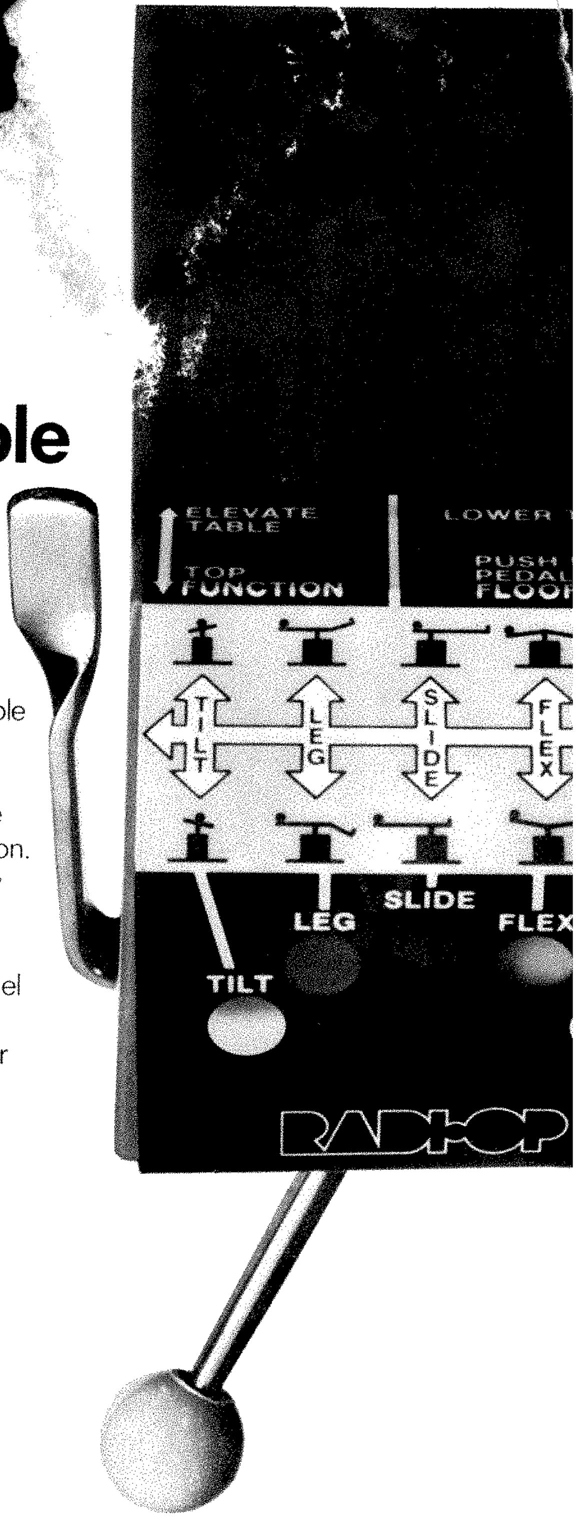

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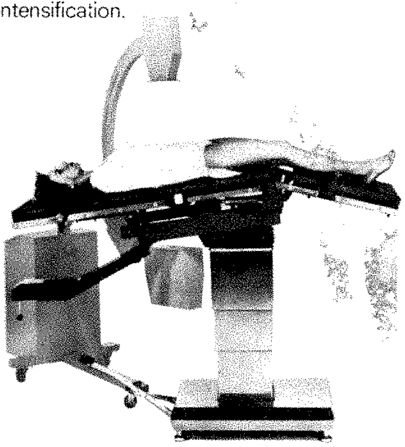

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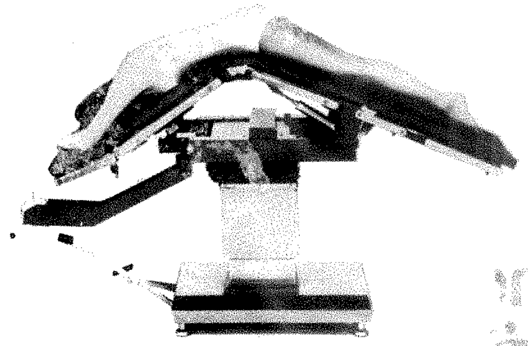

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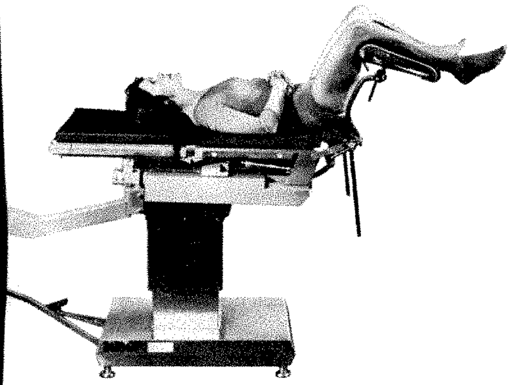

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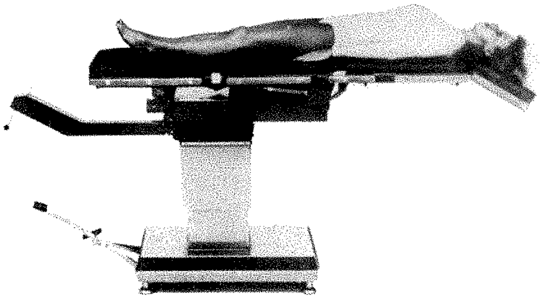

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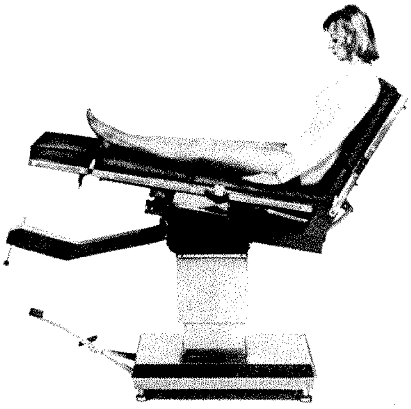

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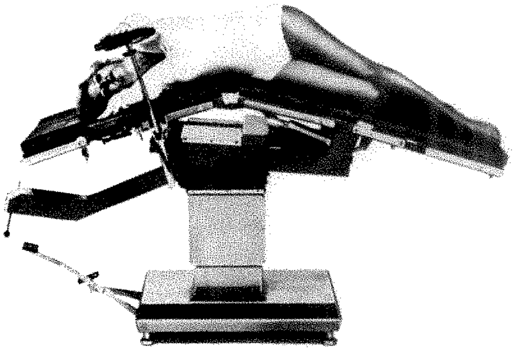

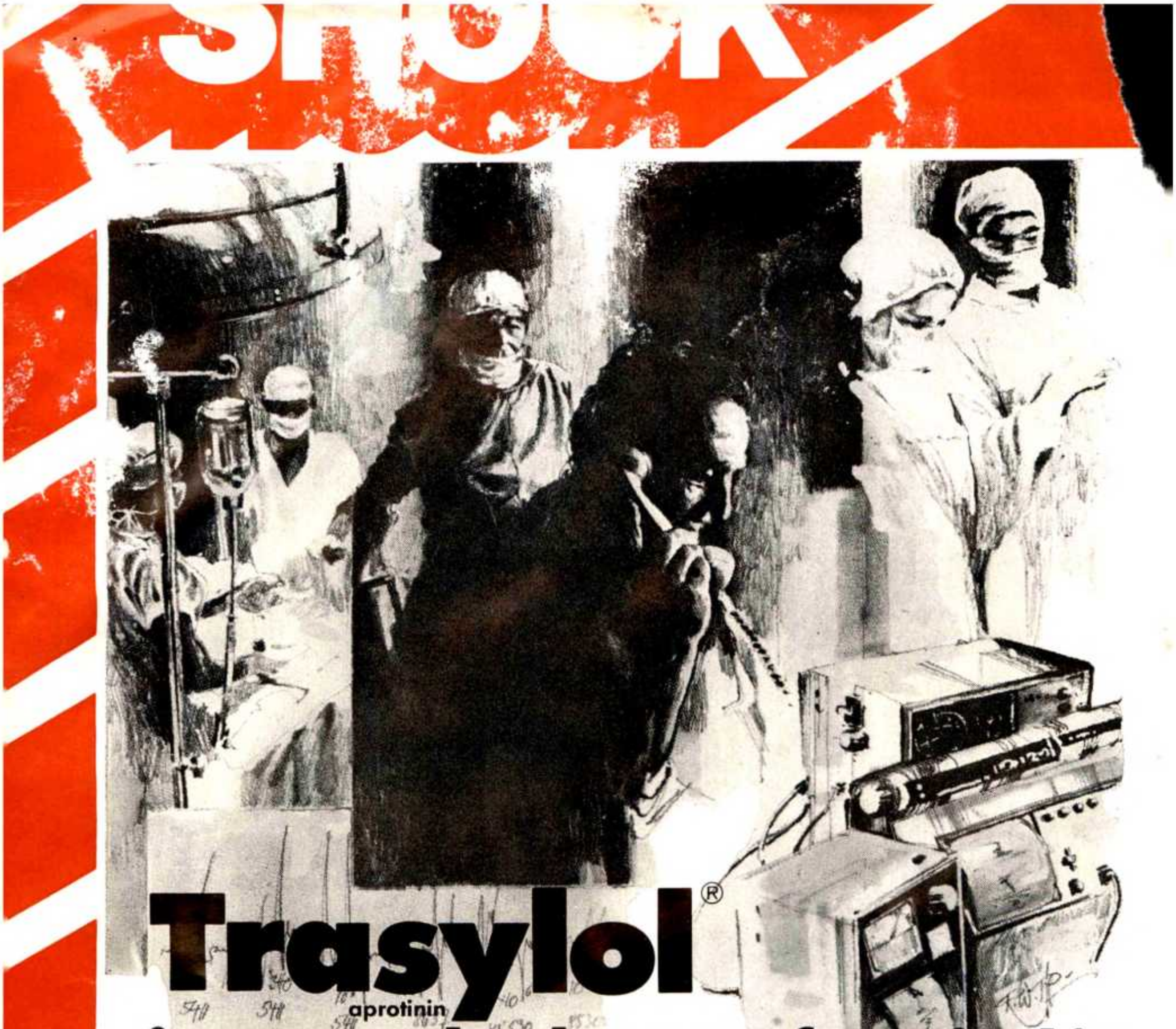

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1) Schneider et al., Chirurg **47,** 185 (1976)
2) McMichan et al., Med. Welt **27,** 2331 (1976)

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the literature. *Am. J. Roentgenol. Radium T* l.
84, 849–860.

EED A., HERI S. A. and BOYER J. L. (1974) Peliosis hepatis associated with androgenic-anabolic steroid therapy. *Ann. Intern. Med.* **81**, 610–613.

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Statistics in *The British Journal of Surgery*

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Spontaneous liver rupture i s nodosa

A. K. C. LI, J. M. RHODES AND A. R. V *

SUMMARY

An unusual case of spontaneous rupture of the liver associated with polyarteritis nodosa is reported.

SPONTANEOUS bleeding into the bowel or kidneys is a well-recognized complication of polyarteritis nodosa (Ostrum and Soder, 1960; Cabal and Holtz, 1971). Haemorrhage into the liver parenchyma has also been reported (Ayers and Fitchett, 1976), but we would like to report what we believe to be the first case of spontaneous rupture of the liver associated with polyarteritis nodosa.

Case report

A 20-year-old Norwegian girl presented with shock and severe generalized abdominal pain of sudden onset. There was no history of trauma and she was not on the contraceptive pill.

Four years previously the patient had been extensively investigated in Norway for iritis, recurrent arthralgia and pyrexia of unknown origin. It had been felt that this was likely to be a collagen disease and she was treated with prednisolone 10 mg a day which she had been taking since that time.

On examination, in addition to shock and signs of generalized peritonism, nodules were felt along both radial arteries. Following resuscitation, laparotomy was performed and 2 l of fresh blood were found in the peritoneal cavity. Arterial blood was seen spurting from a deep 8-cm laceration in the superior aspect of the right lobe of the liver. Suture of the laceration failed to control the arterial haemorrhage and a right hemihepatectomy was performed.

Histology of the resected liver showed only mild centrilobular necrosis attributable to the initial hypotension. Subsequent tests for antinuclear factor, LE cells, Latex test and hepatitis B surface antigen and antibody all proved to be negative. T cell rosetting was found to be severely diminished at 10 per cent (normal 57–73 per cent), indicating severely depressed cellular immunity. The clinical diagnosis of polyarteritis nodosa was confirmed by angiography which demonstrated numerous aneurysms in the mesenteric, renal, hepatic and splenic arteries (*Figs.* 1 and 2).

The patient's postoperative course was stormy, with a right subphrenic abscess which required drainage, oesophageal candidiasis, pneumococcal meningitis and pulmonary infarction. Furthermore, she was hypertensive (BP 230/160) with heavy proteinuria (5 g/24 h). Despite vigorous therapy she died 12 weeks after operation. A post-mortem examination was not performed.

Discussion

Spontaneous liver rupture is known to occur in association with tumours (Caldwell, 1950) and peliosis hepatis (Saeed et al., 1974), but we can find no previous report of this occurrence in association with polyarteritis nodosa, although in one case a hepatic haematoma has been reported (Ayers and Fitchett, 1976). We believe that in our patient rupture of the liver was due to massive bleeding from an aneurysmal intrahepatic artery.

This case demonstrates again the usefulness of angiography in the diagnosis and assessment of polyarteritis nodosa (Ostrum and Soder, 1960).

Acknowledgements

We wish to thank Professor K. E. F. Hobbs, Dr N. McIntyre, Dr R. Dick and Dr Barbara Ansell for their help and advice in the management of this case.

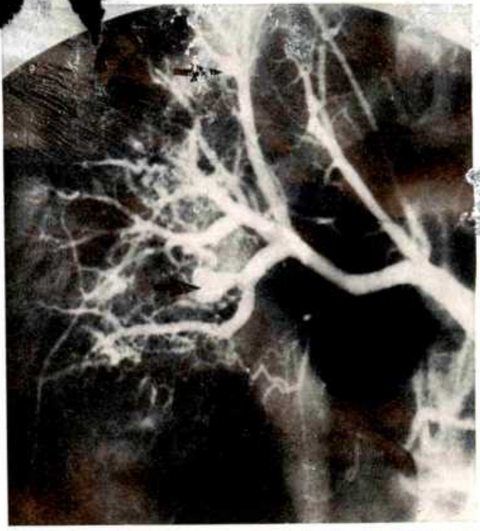

Fig. 1. Right renal arteriogram showing diffusely abnormal small vessel pattern with several discrete aneurysms; a similar appearance was demonstrated in the left kidney.

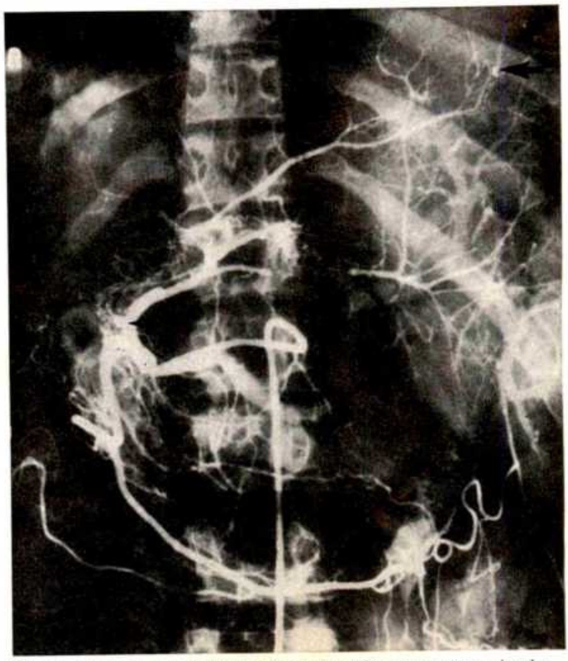

Fig. 2. Hepatic arteriogram demonstrating aneurysms in the residual hepatic arterial territory (after right hemihepatectomy).

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Br Surg. Vol. 66 (979) 251-252

Complete liver dearterializa polvart carcinoid syndrome

GEORGE A. KHOURY, TERRY DIVINE ALEN INI OLT*

SUMMARY

A variety of surgical procedures are available in th treatment of the carcinoid syndrome, the aim being ti destruction of liver secondaries and amelioration symptoms. Dearterialization of the liver may be c sidered when liver secondaries are extensive and me treatment inadequate in controlling symptoms.

The patient reported here had severe symptoms of epigastric pain, anorexia, flushing, diarrhoea and recurrent syncope and was generally deteriorating rapidly. Complete dearterialization of the liver, however, resulted in a dramatic improvement. Now, 2 years later, the patient's hepatic scan, liver function tests and 24-h urine 5-hydroxyindolacetic acid (5-HIAA) are all within normal limits. Destruction of liver secondaries by dearterialization is a relatively simple procedure. Careful attention should be paid to large quantities of pharmacologically active compounds released from the liver during the procedure. Ascites, jaundice and liver cell failure are definite contraindications to surgery.

Carcinoid tumours occur mostly in the gut but they may occur in the biliary tract, lung, bronchi, ovary (Godwin, 1974) and, rarely, at other sites such as the urethra (Sylora et al., 1975). Pearson and Fitzgerald (1949), in reviewing a large series, found metastases in 38 per cent and emphasized that all carcinoids should be considered malignant. The carcinoid syndrome, characterized by flushing, intestinal disturbances and right-sided heart disease, develops in only about 5 per cent of patients with intestinal carcinoid tumour.

Eradication of hepatic metastases is important, as adequate relief of the systemic sequelae of the carcinoid syndrome may not be achieved with conservative therapy. Methods available include hemihepatectomy (Bersohn and Bleloch, 1967; Lannon, 1974), enucleation of tumour deposits (Stephens and Grahame-Smith, 1972) and ligation together with cytotoxic infusion (Murray Lyon et al., 1970; Aune and Schistad, 1972). Complete dearterialization of the liver in the carcinoid syndrome has been performed by McDermott and Hensle (1974) with good results and more recently by Allison et al. (1977) and by Maempel and Modlin (1978) using highly selective cannulation and embolization of the hepatic artery by the Seldinger technique. Their results were encouraging but the reported follow-up was brief.

Case report

A 56-year-old man was admitted in November 1976 with severe disabling symptoms of epigastric pain, anorexia, weight loss, flushing (related to alcohol ingestion), diarrhoea and recurrent attacks of syncope. Seven years earlier a primary ileal carcinoid tumour was resected at laparotomy and multiple secondaries in the liver noted. The patient's symptoms had failed to respond to cyproheptadine, methysergide, alpha- and beta-blockers. He required 25 Palfium tablets daily for pain. On admission he was anaemic (haemoglobin 11·5 g/dl) and cachexic, but despite an enlarged liver, there was no ascites or peripheral oedema. Chest radiographs were clear and a hepatic radioisotope scan revealed a grossly enlarged liver aun cold areas which were consistent with multipl da g. 1). Several 24-h urine collections reveale an f 5-HIAA (*Fig.* 2). Liver function tests were al nal –5). A glucose tolerance test showed a norm ose Selective angiography was performed and th demon the arterial blood supply to the liver ar vascul metastases. However, films obtained were of po quality.

Operation was performed under cover of ampicillin gentamicin. Metronidazole and oral kanamycin were g preoperatively. Through a right paramedian incision abdomen was explored. The liver was found to contain gross deposits diffusely distributed throughout both lobes other metastatic disease was apparent.

Dearterialization of the liver was then carried out by ligat the right, left and common hepatic arteries, together with right gastric and gastroduodenal arteries. All the perito attachments of the liver were divided. The gallbladder removed to prevent ischaemic necrosis. A liver biopsy firmed carcinoid tumour.

The pulse, blood pressure and electrocardiogram wer monitored during the procedure and no change was detected. Peripheral oedema associated with hypoalbuminaemia developed postoperatively, but responded to albumin infusion. Discharge of necrotic material and pus from the wound occurred on several occasions but settled spontaneously. Microscopy revealed necrotic debris and culture was negative There was a small rise in bilirubin and a moderate rise in t liver enzymes, which rapidly returned to normal. The respo of the metastatic tumour is shown by the return of urinary 5-HIAA levels to normal and a dramatic change in liver scan, which returned to normal within 6 weeks (*Figs.* 6 and 7) Symptomatically there was a dramatic response, with immediate disappearance of flushing, diarrhoea and abdominal pain. This remission is continuing to date.

Discussion

Carcinoid tumours are 'apudomas' and are thought to arise from the enterochromaffin (EC) cells of the gut (Welbourn et al., 1974; Pearse et al., 1977). Between 20 and 30 per cent of patients with carcinoids of the small bowel have a second malignant tumour which is totally unrelated (Morgan et al., 1974; Welbourn and Joffe, 1977). The majority of carcinoid tumours secrete 5-hydroxytryptamine (5-HT) together with the enzyme kallikrein, which is responsible for the formation of bradykinin in the blood. These substances are normally carried to the liver by the portal blood and inactivated (Welbourn and Joffe, 1977) but, when large deposits are present, they enter the systemic circulation and cause the carcinoid syndrome (Leading Article, 1975). It is thought that 5-HT is the agent causing diarrhoea, and bradykinin produced from the $alpha_2$-globulin fraction in blood causes the characteristic flush. Although 5-HT is a vasoconstrictor, its actions on the circulation are complex. Furthermore, bradykinin is a vasodilator and may be responsible for the hypotensive attacks (Levine, 1975). Other pharmacologically active substances have been reported in the carcinoid syndrome and they may have a role in the complexity and diversity of the symptoms. Thus, Maempel and Modlin (1978)

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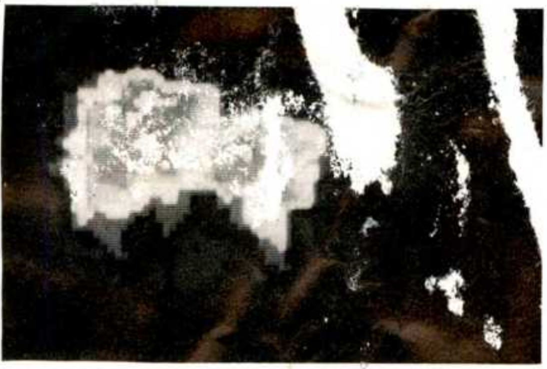

Fig. 1. Front view, 22 Nov. 1976. An enlarged liver, particularly the left lobe, with many ragged indentations on the lower border due to tumour.

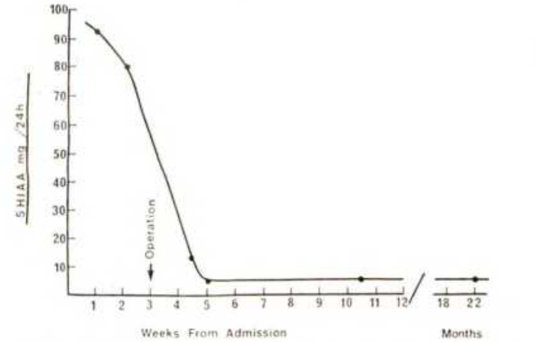

Fig. 2. 5-HIAA levels, showing a dramatic and maintained fall from admission level. (Normal level, <8.)

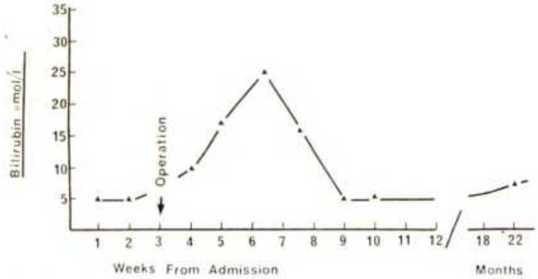

Fig. 3. Bilirubin levels (normal, 5-17 μmol/l).

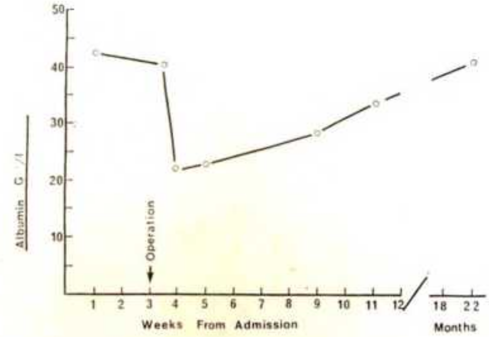

Fig. 4. Albumin levels (normal, 36–52 g/l).

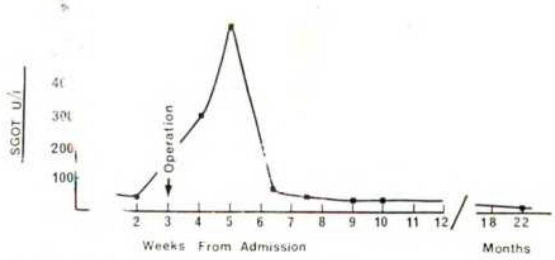

Fig. 5. SGOT levels (normal, 5–54 U/l).

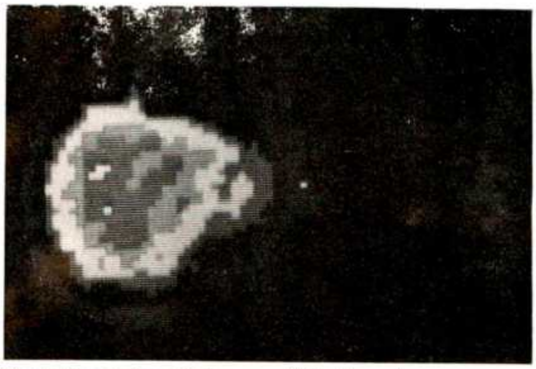

Fig. 6. Front view, 25 January 1977. A small, compact normal liver image.

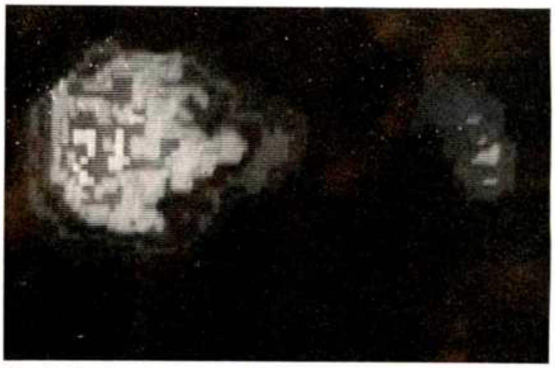

Fig. 7. Front view, 22 August 1978. No significant change seen.

identified for the first time an elevated pancreatic polypeptide in the plasma of a patient with a gastric carcinoid tumour producing mainly 5-hydroxytryptophan (5-HTP), a serotonin precursor.

Diagnosis depends on the presence of 10 mg/day or more of 5-HIAA in the urine; this is estimated according to the method of Udenfriend et al. (1953). High values of 5-HIAA have been reported in non-tropical sprue and after eating fruits, notably bananas, or following ingestion of certain drugs such as phenothiazines (Leading Article, 1975). The drugs chiefly used to relieve symptoms are serotonin antagonists; α-methyldopa for flushing (Welbourn and Joffe, 1977) and methysergide and cyproheptadine for diarrhoea. Ergotamine tartrate, lysergic acid and

'Bol 148', a brominated derivative of LSD [illegible] al., 1955), were tried in the treatment of diarrhoea and flushing but without success. Cytotoxic agents such as cyclophosphamide, 5-fluorouracil and streptozotocin given systemically have brought about remission in some patients. The carcinoid tumour is slow growing and patients often survive 10–20 years (Thorson et al., 1954; Fraser, 1955). Surgery should therefore be considered in the later stages of the illness. Nevertheless, operative treatment should not be postponed until patients are moribund with hepatic cell failure, in which case mortality is markedly increased (Balasegaram, 1972). Although partial hepatectomy is the obvious choice in experienced hands, this procedure is often impossible to perform due to widespread metastases in both lobes of the liver or porta hepatis. Dearterialization of the liver is then indicated.

Breedis and Young (1964) first recognized that malignant tumours in the liver were supplied almost exclusively by arterial blood, whereas normal liver tissue received blood from both the arterial and portal systems. Dearterialization was therefore used in the treatment of many liver tumours, but the procedure carried a high mortality rate since these were terminal cases of primary or secondary carcinoma of the liver (Balasegaram, 1972).

Arterial circulation of the liver has been shown to be re-established within a few days of complete dearterialization (Bengmark and Rosengren, 1970). Nevertheless, necrosis of hepatic tumours occurs following very short periods of arterial ischaemia (Almersjo et al., 1966). Complete dearterialization of the liver is difficult to achieve unless all attachments between the liver and the surroundings are carefully divided except the common bile duct, the portal vein, hepatic veins and inferior vena cava (Bengmark and Rosengren, 1970). Collateral vessels most commonly arise from the inferior phrenic artery or the intercostal arteries. The lesser omentum should be detached from the liver lest an aberrant left hepatic artery be missed (Michels, 1953). Preoperative angiography to show the liver circulation and collaterals is mandatory. Splenoportography is indicated before surgery to exclude thrombosis or portal vein infiltration by tumour (Balasegaram, 1972). A full preoperative work-up should be carried out, including a glucose tolerance test. Feldman et al. (1975) clearly demonstrated that 80 per cent of patients with the carcinoid syndrome had impaired insulin secretion and intolerance to glucose.

During the operative procedure central venous pressure and electrocardiogram recordings should be continuously monitored. Two intravenous infusion routes are preferably kept open to facilitate very rapid fluid or blood replacement should this be necessary. Hypotensive episodes and, occasionally, collapse are reported to occur following anaesthesia and during dearterialization (Levine, 1975; Maempel and Modlin, 1978). Levine suggests the use of either phenylephrine or angiotensin in the treatment of hypotension. Maempel and Modlin administered the antikinin agent aprotinin and steroids during the procedure of embolization and for the following 24 h by continuous intravenous infusion. In addition to these precautions, Allison et al. (1977) gave parachlorophenylalanine 500 mg every 6 h for 48 h before embolization to reduce release of 5-HT during tumour necrosis. Hypotension during hepatic artery [illegible] with a high incidence of hepatic [illegible] (Mays, 1967) and should be [illegible] antibiotic therapy is important in [illegible] emia.

Postopera[illegible] McDermott and Hensle (1974) reported a purulent discharge from the wound which revealed 'ghost [illegible] consistent with carcinoid origin. Similarly, in our patient, a discharge occurred which drained white creamy material for a period of 5 weeks. Microscopy revealed only debris and pus cells. No organisms were grown on culture media.

In patients with the carcinoid syndrome, the availability of the essential amino acid, L-tryptophan is reduced and consequently synthesis of albumin and nicotinic acid may be restricted (Swain et al., 1976). It is noteworthy that our patient developed severe peripheral oedema in the postoperative period. This responded well to albumin infusion and spironolactone therapy.

Finally, liver dearterialization seems to have a place in the treatment of the carcinoid syndrome. Whether this is achieved by embolization as shown recently by Maempel and Modlin (1978), or by surgical means, is a matter of choice, and depends on availability of radiographic expertise. The correct timing of this treatment is important and, although the reported numbers of patients undergoing complete dearterialization are small, we feel encouraged having learned that this patient is now able to run 3 miles each morning, has returned to work and is enjoying a full and active life, 2 years following dearterialization of the liver.

Acknowledgements

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References

ALLISON D. J., MODLIN I. M. and JENKINS W. J. (1977) Treatment of carcinoid liver metastases by hepatic artery embolization. *Lancet* **2**, 1323–1325.

ALMERSJO O., BENGMARK S., ENGERIK L. et al. (1966) Hepatic artery ligation as pretreatment for liver resection of metastatic cancer. *Rev. Surg. (Phila.)* **23**, 377–380.

AUNE S. and SCHISTED G. (1972) Carcinoid liver metastases treated with hepatic dearterialization. *Am. J. Surg.* **123**, 715–717.

BALASEGARAM M. (1972) Complete hepatic dearterialization for primary carcinoma of the liver. *Am. J. Surg.* **124**, 340–345.

BENGMARK S. and ROSENGREN K. (1970) Angiographic study of the collateral circulation to the liver after ligation of the hepatic artery in man. *Am. J. Surg.* **119**, 620–624.

BERSOHN I. and BLELOCH J. (1967) Right hemihepatectomy in secondary carcinoid of the liver: clinical course and liver function tests. *S. Afr. Med. J.* **1**, 271–274.

BREEDIS C. and YOUNG G. (1964) The blood supply of neoplasms in the liver. *Am. J. Pathol.* **31**, 969–985.

FELDMAN J. M., PLONK J. W., BIRENS C. H. et al. (1975) Glucose intolerance in the carcinoid syndrome. *Diabetes* **24**, 664–667.

FRASER I. (1955) Argentaffinoma (carcinoid tumour) with cyanosis. *Lancet* **2**, 174–175.

GODWIN J. D. (1974) Carcinoid tumours—an analysis of 2837 cases. *Cancer* **36**, 560–569.

LANNON J. (1974) Seventeen cases of hepatectomy. *S. Afr. J. Surg.* **12**, 227–232.

LEADING ARTICLE (1975) Diagnosis of malignant carcinoid syndrome. *Br. Med. J.* **3**, 122–123.

EVINE R. J. (1975) Diagnosis an carcinoid syndrome. *JAMA* 23

DERMOTT W. V. and HENSLE T. W noi of the liver treated by hepa. *Su* **180**, 305–308.

MPE Z. and MODLIN I. 978) me of a gastric carcin tum atic ta *r. Surg.* **65**, 51 20.

1967) Observatio nd manag arter ligation. *Surg. G ecol. Obstet.* 2 –204.

CHELS N. A. (1953) Collateral arterial y o the liver after ligation of the hepatic artery removal of the coeliac axis. *Cancer* **6**, 708–724.

GAN J. G., MARKS C. and HEARN D. (19 4) *Ann. Surg.* **18** 720–727.

AY-LYON I., DAWSON J. and PARSONS V. (1970) Treatment of secondary hepatic tumours by ligation of hepatic artery and infusion of cytotoxic drugs. *Lancet* **2**, 172–175.

E A. G. E., POLAK J. M. and BLOOM S. R. (1977) The newer ut hormones: cellular sources, physiology, pathology and linical aspects. *Gastroenterology* **72**, 746–757.

C. M. and FITZGERALD P. J. (1949) Carcinoid tumours re-emphasis of their malignant nature, review of 140 es. *Cancer* **2**, 1005–1026.

P. J. D., LENNARD-JONES J. E. and CURZON G. et al. (1955) Humoral effects of metastasising carcinoid tumours. *Lancet* **2**, 1004–1009.

and GRAHAME-SMITH D. (1972) Treatment of d syndrome by local removal of hepatic meta- *roc. R. Soc. Med.* **65**, 444–449.

A H., DIAMOND H. M., KAUFMAN M. et al. (1975) Primary carcinoid tumour of the ureth *J. Urol.* **114**, 150–153.

N C. D., TAVILL A. S. and NEALE G. (1976) Studies of tryptophan and albumin metabolism in a patient with carcinoid syndrome, pellagra and hypoproteinaemia. *Gastroenterology* **71**, 484–489.

SON A., BIORCK G., BJORKMAN G. et al. (1954) Malignant carcinoid of small intestine with metastases to liver, valvular disease of right side of heart (pulmonary stenosis and triscuspid egurgitation without septal defects), peripheral or tor symptoms, bronchoconstriction and unusual of cyanosis; clinical and pathological drome. *n. Heart. J.* **47**, 795–817.

UDENFRIEND S., CLARK C. T., TITUS E. O. (1953) *Fed. Proc.* **12**, 282.

WELBOURN R. B. and JOFFE S. N. (1977) The apudomas. In: TAYLOR S. (ed.) *Recent Advances in Surgery*. Edinburgh, Churchill Livingstone, pp. 311–334.

WELBOURN R. B., PEARSE A. G. E., POLAK J. M. et al. (1974) The apud cells of the alimentary tract in health and disease. *Med. Clin. North Am.* **58**, 1359–1374.

Paper accepted 10 November 1978.

ave been no episodes of c [illegible] fit and active and has ga [illegible] height since the operation.

[illegible] specimen consisted of the enlarged gall [illegible] a [illegible] herent 3-cm mass encasing the common he [illegible], [illegible] and common bile ducts (*Fig.* 2). The cystic duct was completely occluded and a probe was passed through the common hepatic and common bile ducts with difficulty. The tumour was encapsulated, a mottled yellow-brown in colour and had a soft centre. Sections of the encased bile duct showed patchy loss of epithelial lining, loss of muscle coat and replacement by collagenous fibrous tissue. There were foci of acute inflammatory cells around the bile duct remnants. Sections [illegible] surrounding tumour bulk showed similar sheets of collagenous fibrous tissue with a mixed inflammatory cell infiltrate (*Fig.* 3). Within the central mass of tumour there [illegible] a large area of lymphoid tissue with reactive follicular hyperplasia.

ssion

istological features of this lesion are unusual and not described in standard texts. They are, however, similar to a single case previously reported by ith et al. (1964), who described a histologically benign mass surrounding the distal common bile duct in a 6-year-old boy. Because of its tumour-like appearance at operation, excision was by pancreatico-duodenectomy. The lesion was spherical, 3 cm in diameter, with a firm, yellow-tan cut surface. The tumour mass was entirely benign, being composed of bundles of fibroblasts and collagen fibres with large numbers of chronic inflammatory cells scattered throughout. The encased bile duct showed loss of epithelium with dense surrounding fibrous tissue. On the basis of these microscopic findings, these authors ed t [illegible] ion ‘an inflammatory pseudotumour’ of [illegible] common bile duct.

[illegible] these microscopic and histological features accord [illegible] those of the tumour presented in this paper, [illegible] we believe is a second case of this histologically [illegible] lesion. The location of the tumour reported [illegible] in the proximal part of the extrahepatic biliary tr [illegible] probably accounts for the well-defined area of ly[illegible] id tissue with follicular hyperplasia which mi[illegible] represent the cystic lymph gland. The aetiology of [illegible] tumour must be speculative, but it seems to rep[illegible] an excessive inflammatory reaction to some loc[illegible] irritant that might be chemical or infective in nature. One further possibility might be that the lesion represents a form of sclerosing cholangitis, though its localized nature would be unusual as would the loss of bile duct epithelium and the encapsulated nature of the tumour. In addition, the child reported here has remained well in the 21 months of follow-up.

The prognosis would seem to be excellent and relate not to the tumour, which is histologically benign, but to the technical problems involved in surgical resection and reconstitution of biliary drainage.

References

HAITH E. E., KEPES J. J. and HOLDER T. M. (1964) Inflammatory pseudotumour involving the common bile duct of a six-year-old: successful pancreatico-duodenectomy. *Surgery* **56**, 436–441.

OKUDA K., TANIKAWA K., EMURA T. et al. (1974) Non-surgical percutaneous transhepatic cholangiography—diagnostic significance in medical problems of the liver. *Am. J. Dig. Dis.* **19**, 21–36.

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Surg. Vol. 66 (1979) 257-

Benign inflammatory tum mon bile duc

J. D. STAMATAKIS, E. R. HOWARD A LL AMS

SUMMARY

A rare cause of obstructive jaundice in childhood presented. Ultrasound and subsequent percutaneou cholangiography demonstrated the te of obstructio Histological examination of the re ted tumo showed features consistent with a diag is of beni inflammatory tumour of the common bile duct.

A CASE of obstructive jaundice in a child resulting from encasement of the extrahepatic biliary tree by an inflammatory mass is described. The obstructing lesion, which at surgery closely simulated a tumour, has been reported only once previously, being described on that occasion as an inflammatory 'pseudotumour' of the bile duct (Haith et al., 1964).

Case report

A previously fit 13-year-old girl was referred because of jaundice and abdominal pain of 12 weeks' duration. The stools were pale and the urine dark. On examination she was deeply jaundiced, though without the stigmas of chronic liver disease. The liver was smooth, tender and enlarged to mid-way between the costal margin and the umbilicus. The gallbladder was palpable. There were no other abnormal physical signs.

Full blood count and film, autoantibodies, HBsAg, serum proteins and blood chemistry were normal. Prothrombin time was not prolonged (vitamin K given before referral), ESR 81 mm/h, bilirubin 230 μmol/l, alkaline phosphatase 1400 i.u./l and aspartic acid transaminase 166 i.u./l. Abdominal ultrasound revealed a solid mass around the common hepatic and common bile ducts. Hepatic arteriography showed a faint blush below the liver, suggesting a relatively avascular tumour. Percutaneous cholangiography with a fine-needle technique (Okuda et al., 1974) demonstrated that the biliary system was dilated to a point in the common hepatic duct at which there was complete hold-up of contrast medium with intraluminal shouldering (*Fig.* 1). The gallbladder was not visualized.

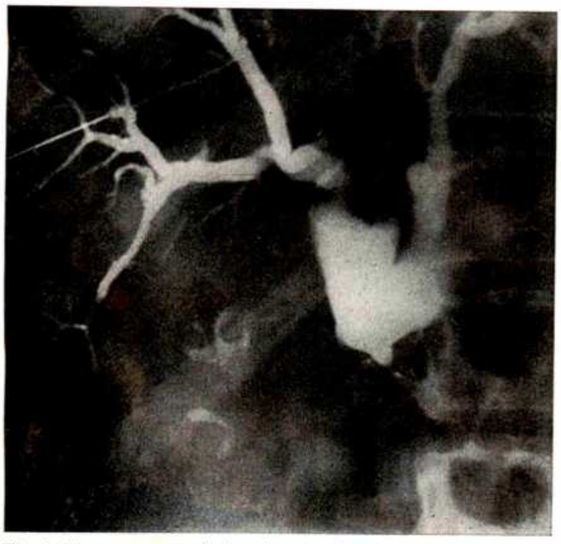

Fig. 1. Percutaneous cholangiogram showing a dilated intrahepatic biliary tree and common hepatic duct. There is complete hold-up of contrast medium in the distal common hepatic duct.

f oper on a distended ga ladder was first aspirated clear mucus. There was a 3-cm spherical tumour closely applie to the porta hepatis and involving the upper common bile duc cystic duct and common hepatic duct. The tumour w excised with the common hepatic and common bile ducts a he confluence of the right and left hepatic ducts was drai by a 25-cm Roux-en-Y loop of jejunum. In addition, a l accessory right hepatic duct required separate implanta into the Roux loop. The child made an uneventful reco from this procedure and was maintained on intermittent a biotic therapy for 1 year. Since this was stopped 9 months

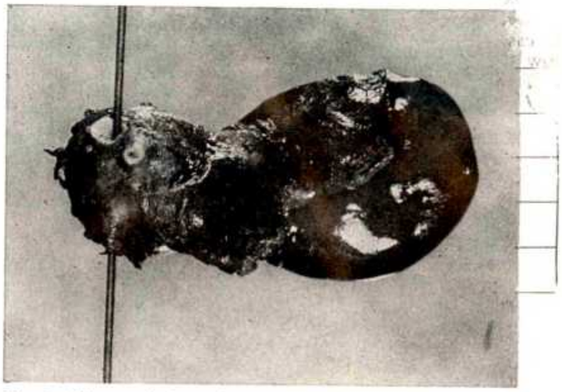

Fig. 2. The surgical specimen: posterior view to show the distended gallbladder (left) and spherical tumour surrounding the common hepatic, cystic and common bile ducts. The probe passed through the common hepatic and common bile ducts. (Scale in centimetres.)

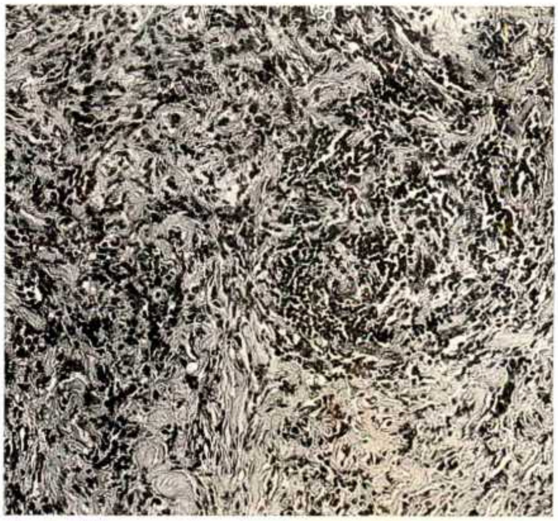

Fig. 3. Collagenous tissue found encasing the common bile duct with a moderate infiltrate of chronic inflammatory cells. (HE. × 95.)

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* King's College Hospital, London.

Hepatic artery aneurysm [illegible]ary surgery

A. HUBENS AND A. DE SCHE[illegible]ER*

SUMMARY

This paper describes a patient operated upon f[illegible]l-bladder and bile duct stones, who presented [illegible] an extrahepatic aneurysm of the main hepatic [illegible]ial trunk and with a central intrahepatic haematoma assumed to be caused by the rupture of [illegible] intrahepatic aneurysm or by secondary intrahepatic necrosis. Exploration of the bile ducts resulted in haemobilia. The presence of extrahepatic arterial collaterals precluded individualization of the left and right hepatic arteries and subsequent distal arterial ligation or partial hepatectomy. Ligation of the common hepatic artery, although initially successful, was insufficient to avoid a recurrent and fatal haemobilia.

ANEURYSMS of visceral branches of the abdominal aorta are rare. The greatest number of these aneurysms involve the splenic (46·9 per cent) and the hepatic (16·2 per cent) arteries. Lataste et al., reviewing the world literature on aneurysms of the hepatic artery in 1971, stated that about 250 cases had been reported at that time. Aneurysm of the hepatic artery is an uncommon entity and the diagnosis is seldom made preoperatively, especially when the patient presents with bile duct stones which could explain his complaints. Angiography may identify the lesion but the majority of hepatic aneurysms have been discovered at post-mortem examination. About 60 cases have been successfully managed by surgery (Harlaftis and Akin, 1977). Hepatic aneurysms constitute a pitfall in diagnosis and treatment, and they may give rise to serious complications in biliary surgery, as described in the following case report.

Case report

A 69-year-old man was admitted to the surgical wards of Stuivenberg Hospital, Antwerp, on 20 June 1977. He complained of attacks of colicky pain in the right hypochondrium during the previous 4 weeks, radiating to the back and occurring mainly after fatty meals. He had never experienced such pains before. In his past history there were no symptoms of previous abdominal illness. He had never been jaundiced or sustained any abdominal trauma. He had had an operation for an inguinal hernia several years previously. He did not drink or smoke and had always lived in Western Europe.

Examination revealed a pale, thin man, who was afebrile and anicteric. The abdomen was flat and not tender. A recurrent right inguinal hernia was present. No other abnormal masses were felt. The liver and spleen were not palpably enlarged and further physical examination was normal.

The red blood cell count on admission was $4{\cdot}2\times10^{12}$/l, the white cell count $7{\cdot}2\times10^{9}$/l with 58 per cent polymorphonuclear cells. An intravenous cholangiogram demonstrated several stones in the gallbladder and, in addition, one in the distal bile duct. At the same time a calcified, oval structure about 1 cm in length was visible, medial to the porta hepatis (*Fig.* 1).

On 22 June 1978 laparotomy for removal of the gallstones was performed. The gallbladder was not inflamed and contained several stones. The common hepatic duct was surrounded by a net of pulsating vessels. A firm, nodular structure could be palpated in the medial part of the lesser omentum. A tentative diagnosis of aneurysm of the hepatic artery with collateral circulation to the porta hepatis was made.

A peroperative cholangiogram was performed via the cystic duct, which confirmed the presence of a stone in the distal bile duct. The common bile duct was freed from the surrounding arterial branches and choledochotomy was performed. The bile duct contained some 'mud' and a stone was extracted by means of Desjardins forceps. On exploring the left and the right hepatic ducts with a Fogarty biliary balloon catheter, haemorrhage occurred into the lumen of the bile ducts, but this ceased spontaneously after a few minutes.

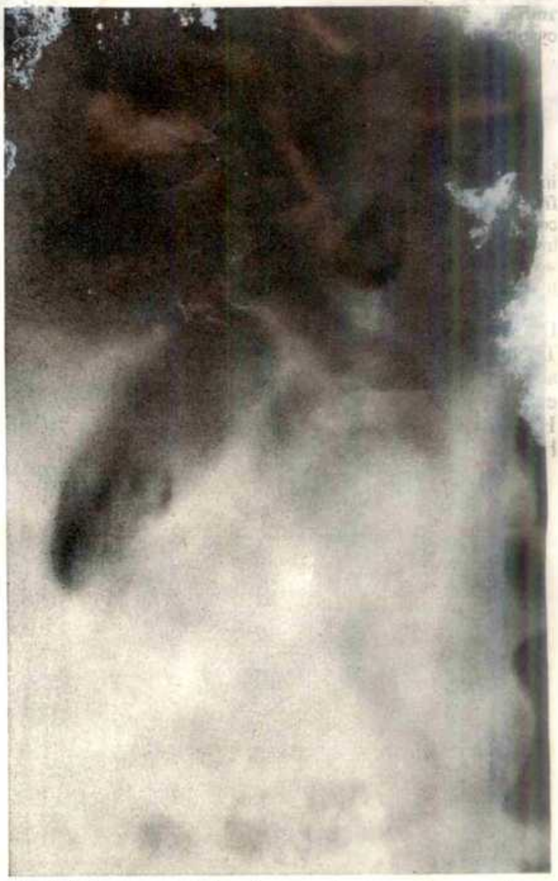

Fig. 1. Intravenous cholangiogram showing a stone in the distal bile duct and a calcified oval structure medial to the porta hepatis.

Retrograde cholecystectomy was performed and a T tube inserted in the common bile duct to allow biliary decompression. The subhepatic space was drained by a multitubular drain brought out through a small incision opposite the tip of the eleventh costal cartilage.

During the first postoperative week the patient's progress was uneventful and haemorrhage did not recur. On 1 July 1978 a cholangiogram was performed via the T tube drain. This demonstrated not only the absence of intraductal stones but also a progressive extravasation of contrast medium in a centrally located intrahepatic cavity. Immediately after cholangiography brisk bleeding commenced through the long arm of the T tube and also via the abdominal drain.

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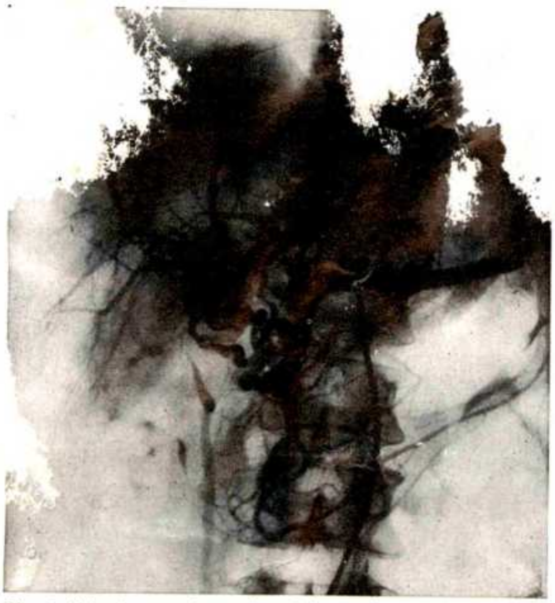

Fig. 2. Selective arteriography of the coeliac trunk showing that the extrahepatic aneurysm stops the main blood flow to the liver which is irrigated by vessels originating from the coeliac trunk.

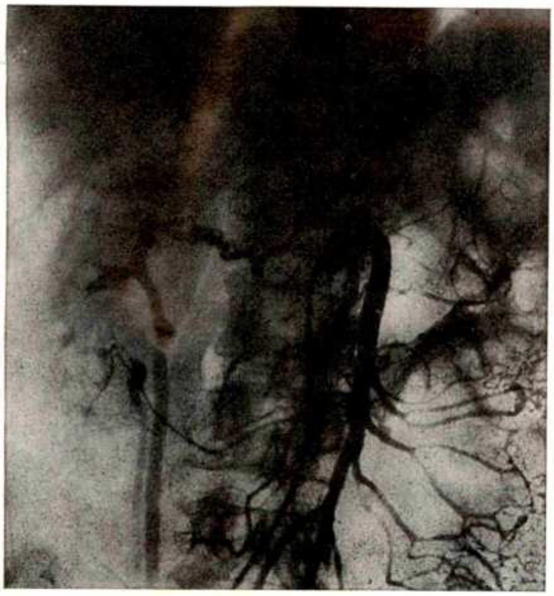

Fig. 3. Selective arteriography of the superior mesenteric artery showing the calcified aneurysm and collateral vessels to the liver originating from the superior mesenteric artery. A central intrahepatic haematoma displaces the blood vessels.

Three units of blood were transfused and the condition of the patient improved. Selective arteriography of the coeliac trunk and the superior mesenteric arteries was carried out. These studies demonstrated the presence of a thrombosed aneurysm of the hepatic artery. The liver was supplied by a net of collateral vessels, originating mainly from the coeliac trunk but also from the superior mesenteric artery. Distal to the thrombosed artery a large cavity was demonstrated, located in the central part of the liver at the bifurcation of the

ures (*Figs.* 2, 3). On 9 July 1977 the patient presented recurrent haemorrhage through the drains. Repeated sions were unable to stabilize his condition. Emergency my was undertaken. On opening the abdomen, the ic space was observed to be filled with clot. The of arterial collaterals precluded elective clamping of tructures, and the central liver cavity appeared to be nd too centrally located to be opened in order to leeding vessels without immediately endangering ife. The only apparent way to control the situa- be to lig e the main arterial supply to the liver. patic artery was ligated at its origin from the a oximal to the collateral vessels. The active lin but immediately after this procedure, the nt in iced. Hepatic function was lowest on 15 bu radually thereafter as did the patient's gen .

On 30 patient developed a new, acute haemorrhagic episode. He pr nted with melaena and bled massively via the drains. Emergency endoscopy confirmed the absence of gastrointestinal ulceration but demonstrated active bleeding through the ampulla of Vater. Despite massive transfusion (20 units) the patient died in hypovolaemic shock on 1 August 1977.

A post-mortem examination confirmed the peroperative findings. The distal portion of the hepatic artery was occluded by a calcified and thrombosed aneurysm. A large net of collaterals had developed towards the liver and the hepatic artery was ligated at its origin, proximal to these collaterals. A vast, necrotic, haemorrhagic cavity occupied the central portion of the liver and communicated with the right hepatic duct. The whole intestinal tract was filled with blood from the ampulla of Vater downwards. No oesophageal varices or gastroduodenal ulceration could be demonstrated.

Discussion

The world literature on aneurysm of the hepatic artery has been extensively reviewed by Guida and Moore (1966), Deterling (1971) and Erskine (1973). Two main types of aneurysm occur—saccular and dissecting. Saccular aneurysms occur most frequently. They may be congenital or secondary to acquired disease such as atherosclerosis, infection or trauma. Dissecting aneurysms may be primary and restricted to the involved artery, but sometimes they are secondary, presenting as a complication of the relatively common dissecting aneurysm of the aorta (Hill and Edwards, 1974). Most aneurysms are single but some patients do present with multiple aneurysms of the visceral abdominal arteries.

Two-thirds of the reported cases have been extrahepatic. They may rupture into the free peritoneal cavity or into an adjoining structure—the bile ducts, gall bladder, duodenum or portal vein. Perforation into the bile ducts leads to haemobilia, characterized by gastrointestinal bleeding, biliary colic and jaundice. Perforation into the peritoneal cavity followed by shock is relatively frequent.

Intrahepatic aneurysms are less frequent and less well known. The right hepatic artery is more frequently involved than the left. Rupture of an intrahepatic aneurysm may cause the formation of an intrahepatic haematoma. Erskine (1973) reported a patient presenting with an intrahepatic haematoma that had been caused by a ruptured aneurysm that resolved spontaneously. Generally speaking, however, these haematomas lead to a rupture of the liver capsule with secondary intraperitoneal bleeding.

Symptoms before rupture has occurred are nonspecific and may even be absent. Selective angiography of the coeliac axis or the superior mesenteric artery is at present the most reliable diagnostic tool. This investigation is mandatory in any case in whic[illegible] clinical history of haemobilia or the presence [illegible] calcified shadow in the liver area on X-ray ex[illegible]tion suggests the possibility of a hepatic [illegible] aneurysm. Moreover, selective angiograp[illegible] localize the aneurysm precisely and may be of importance in planning its management.

The treatment of an aneurysm of the hep[illegible] especially the intrahepatic variety, is still [illegible] discussion. Ligation of the hepatic arter[illegible] with excision of the aneurysm are [illegible] n[illegible] commonly employed procedures (Har[illegible] A[illegible] 1977; Taylor and Dawson, 1978). In [illegible] case[illegible] graft reconstruction has been performe[illegible] [illegible]xcision of the aneurysm (Danielson et al., 196[illegible] R[illegible]ten and Sikkenk, 1971; Goldman and Stone, 1974). Some patients have been successfully treated by percutaneous embolization of a branch of the hepatic artery (Goldblatt et al., 1977).

Survival following hepatic artery ligation depends on increased extraction of oxygen from the portal blood as well as on the remaining arterial supply to the liver (Madding and Kennedy, 1972). A rapid development of collateral vessels has been demonstrated by angiographic studies in man (Bengmark and Rosengren, 1970). According to Mays (1967), the increased extraction of oxygen from portal venous blood appears to be the major compensatory mechanism after hepatic arterial flow is cut off. Factors which reduce portal venous flow or increase hepatic oxygen requirements should be avoided.

When the hepatic aneurysm is proximal to the gastroduodenal artery, an excision may be safely performed. The gastroduodenal artery will then supply the liver with arterial blood from the superior mesenteric artery via the pancreaticoduodenal arcades. When the extrahepatic aneurysm is distal to or on the gastroduodenal artery, reconstruction of the arterial blood flow to the liver after excision of the aneurysm is mandatory. This may be performed by a direct anastomosis, by a vascular graft, by mobilization of the splenic artery or by endo-aneurysmorraphy. A trial period of arterial occlusion and observation of the liver for colour changes may give useful information as to whether a reconstruction of the interrupted arterial flow is necessary (Erskine, 1973).

When the aneurysm is intrahepatic, and moreover when it has caused an intrahepatic haematoma or haemobilia, management is a delicate problem. Knowledge of the exact location of the lesion is essential in order to proceed either to ligation of the right or left branch of the hepatic artery or to excision of the involved liver segment or lobe.

Reconsidering the case history of our patient, it is highly probable that he presented with a simultaneous ruptured intrahepatic aneurysm and an obliterating extrahepatic aneurysm on the distal hepatic artery, as well as bile duct stones.

A space-occupying intrahepatic lesion displacing bile ducts and blood vessels was shown on peroperative cholangiography as well as on post-operative selective angiography. Peroperative exploration and post-mortem examination proved this lesion to be a cavity filled with blood, assumed to be a ruptured intrahepatic aneurysm. Nevertheless, one must admit that the impairment of the arterial flow to the liver might also have been responsible for the development of secondary intrahepatic necrosis, th[illegible]ation of this central [illegible] [illegible]. [illegible]ative [illegible]ration of the [illegible] [illegible]ulted in [illegible] communication betw[illegible] [illegible] duct and the intrahepatic [illegible] [illegible]ing in haemobilia. The treatment of [illegible] [illegible]es either the ligation of the bleeding [illegible] excision of the involved liver segment or lobe (Taylor and Dawson, 1978).

An attempt to locate the central intrahepatic haematoma was not successful in practice. Owing to the obliterating extrahepatic aneurysm on the distal hepatic artery and the collateral circulation to the porta hepatis, neither the right nor the left hepatic artery could be individualized on angiographic examination, nor could they be electively clamped during surgical exploration.

Wilkinson et al. (1968) reported 3 cases of post-traumatic haemobilia which responded favourably to ligation of the common hepatic artery, but various authors have pointed out that not all patients with intrahepatic bleeding due to ruptured aneurysm will be controlled by such means (Bruwer and Hollenbeck, 1957; Guynn and Reynolds, 1961; Erskine, 1973).

References

BENGMARK S. and ROSENGREN K. (1970) Angiographic study of the collateral circulation to the liver after ligation of the hepatic artery in man. *Am. J. Surg.* **119**, 620–624.

BRUWER A. J. and HOLLENBECK G. A. (1957) Aneurysm of the hepatic artery: roentgenologic features in one case. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **78**, 270–272.

DANIELSON G. K., DAVIS N. P., GRIFFEN W. O. et al. (1968) Successful resection of distal hepatic artery aneurysm with graft reconstruction of the hepatic arteries. *Surgery* **63**, 722–726.

DETERLING R. A. (1971) Aneurysm of the visceral arteries. *J. Cardiovasc. Surg.* **12**, 309–322.

ERSKINE J. M. (1973) Hepatic artery aneurysm. *Vasc. Surg.* **7**, 106–125.

GOLDBLATT M., RAD F. F., GOLDIN A. R. et al. (1977) Percutaneous embolization for the management of hepatic artery aneurysms. *Gastroenterology* **73**, 1142–1146.

GOLDMAN B. S. and STONE R. M. (1974) Aneurysm of the hepatic artery. Reconstruction with autogenous saphenous vein. *J. Cardiovasc. Surg.* **15**, 692–695.

GUIDA P. M. and MOORE S. W. (1966) Aneurysm of the hepatic artery. Report of five cases with a brief review of the previously reported cases. *Surgery* **60**, 299–309.

GUYNN V. L. and REYNOLDS J. T. (1961) Surgical management of haemobilia. *Arch. Surg.* **83**, 73–81.

HARLAFTIS N. N. and AKIN J. T. (1977) Hemobilia from ruptured hepatic artery aneurysm. Report of a case and review of the literature. *Am. J. Surg.* **133**, 229–232.

HILL D. E. and EDWARDS J. E. (1974) Primary dissecting aneurysm of the hepatic artery. *Arch. Intern. Med.* **133**, 471–474.

LATASTE I., ALBOND J. C. and MELET I. (1971) Anéurysme intra-hépatique compliqué d'hémobilie, guéri par hépatectomie droite. *Presse Med.* **79**, 1809–1811.

MADDING G. F. and KENNEDY P. A. (1972) Hepatic artery ligation. *Surg. Clin. North Am.* **52**, 719–728.

MAYS E. T. (1967) Observations and management after hepatic artery ligation. *Surg. Gynecol. Obstet.* **124**, 801–807.

RUTTEN A. P. M. and SIKKENK P. J. H. (1971) Aneurysm of the hepatic artery: reconstruction with saphenous vein-graft. *Br. J. Surg.* **58**, 262–266.

TAYLOR S. A. and DAWSON J. L. (1978) The treatment of haemobilia. *Br. J. Surg.* **65**, 252–253.

WILKINSON G. M., MIKKELSEN W. P. and BERNE C. J. (1968) The treatment of post-traumatic hemobilia by ligation of the common hepatic artery. *Surg. Clin. North Am.* **48**, 1337–1346.

Paper accepted 30 October 1978.

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A study of arterial prostheses by scanning electron microscopy

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SUMMARY

Scanning electron micrographs were taken of ten different vascular prostheses. The micrographs showed that some prostheses were damaged and some had traces of chemicals on their surface. The application of standard vascular clamps damaged most grafts and some showed remarkable changes on resterilization.

MOST arterial prostheses are made from synthetic fibres, usually Dacron or Teflon, and a new generation of prostheses for large arteries has recently become available, specifically made to have a higher porosity than their predecessors. There is now a wide choice of prostheses; the differences between them are small and selection tends to be arbitrary. As part of a larger project to compare the mechanical properties of the various prostheses we took photomicrographs of their surfaces and investigated the effects on them of resterilization.

Materials and methods

Specimens of fabric were chosen from amongst batches of prostheses supplied to the hospital by the manufacturers. They were all sterile and ready for implantation.

The samples were coated with a layer of gold atoms by the process of sputter coating (Allan and Simmens, 1976). Particles of atomic dimensions are ejected from a target cathode as a result of momentum transfer between incident ions (gas ions accelerated by a high voltage) and the target. These particles traverse a vacuum chamber and are deposited on the specimen as a thin film.

Several samples from each prosthesis, each approximately 0·25 cm² in surface area, were mounted without tension, and with either the inner surface or the outer surface uppermost.

We used a Jeol JFMI scanning electron microscope in conjunction with a Mamiya camera and 127 film. Several photographs were taken of each sample of fabric at magnifications of ×33, ×100, ×1000, ×3000 and ×10 000. The photographic prints were in black and white and measured 18×14·5 cm.

To examine the effects of sterilization, lengths of each prosthesis were cut into three pieces; one piece was sterilized once, another twice and the third piece three times. To obtain a picture of each prosthesis in cross-section the outer surface of a sample of prosthesis was marked before embedding it in Silastic. Samples were embedded under various degrees of tension. They were then cut lengthways (i.e. perpendicular to the crimp) and mounted with the cut surface exposed. The size of the interstices between bundles of yarn (pore size) and the roughness of the internal surface could be estimated from photographs of these preparations.

Results

We examined seven types of prosthesis made from Dacron, two from Teflon and one made of expanded polytetrafluoroethylene (PTFE). 1, Cooley double velour knitted Dacron; 2, Cooley knitted Dacron; 3, DeBakey knitted Dacron; 4, DeBakey woven Dacron; 5, DeBakey Vasculour 'D' internal velour knitted Dacron; 6, DeBakey 'Ultra Lightweight' knitted Dacron; 7, Sauvage double velour knitted Dacron; 8, Edwards knitted Teflon; 9, Edwards woven Teflon; 10, Gore-Tex (expanded PTFE).

Gore-Tex prostheses are dissimilar to all the others in that they are made from expanded polytetrafluoroethylene rather than being woven or knitted. A layer of expanded PTFE was seen to be sandwiched between two outer skins, also made from PTFE but of a different composition. When this prosthesis was clamped [illegible] compression marks were visible to the naked eye (*Fig.* 1). Microscopically, the fibres were found to be compressed with no intervening spaces. All the other prostheses were made of fibres with a circular cross-section except for the Cooley double velour. This prosthesis was made up of two shapes of fibres, one having a circular cross-section and one having a trilobal cross-section. At high magnification (×10 000) the fibres of this prosthesis were found to have traces of a finish on the surface (*Fig.* 2). Successive extractions with boiling solvents, water, petroleum ether, acetone, methanol and toluene removed very small amounts of material. These were identified by infrared spectroscopy as polyester oligomer and what was almost certainly a spinning or knitting lubricant containing tallow. A finish was also detected on the surface of the Edwards knitted Teflon graft.

The fibres of some prostheses were damaged, principally on the ridges of both the inside and the outside surfaces, where they appeared to be crushed and split. This type of damage was most marked in samples of woven Teflon and was present in all the Teflon prostheses we examined (*Fig.* 3). In addition, tiny strands of Teflon were found to stretch between the fibres and across the surface of the individual fibres. These microfibres were only seen at a high magnification (×3000).

There was little or no change in most prostheses after resterilization, but the Cooley knitted Dacron graft showed remarkable changes. When the prosthesis was first examined the surfaces of individual fibres were smooth except for a few crystals of cyclic oligomer. After a further resterilization a few more crystals appeared on the surface, and after three resterilizations the fibres appeared to be coated with a thick layer of crystals (*Figs.* 4 and 5). Other Dacron grafts were not affected in this way although the fibres were apparently similar before resterilization.

Clamping the knitted and woven prostheses did not damage the individual fibres, but it did slightly crush the knit or weave, changing the structure of the interstices.

Discussion

The method of manufacture is fairly standard—synthetic fibres are extruded and then spun together to form a yarn. The shape of the fibres is determined by the shape of the nozzle through which they are

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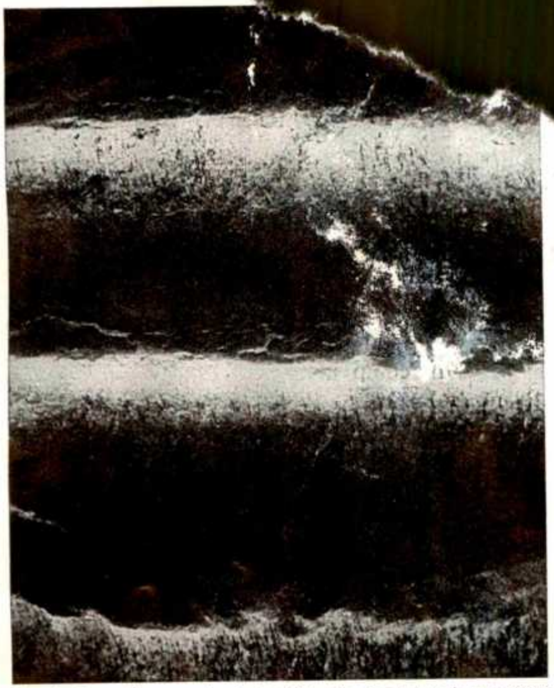

Fig. 1. Gore-Tex prosthesis (× 52). The dark bands represent areas where the teeth of a DeBakey arterial clamp have crushed the fabric.

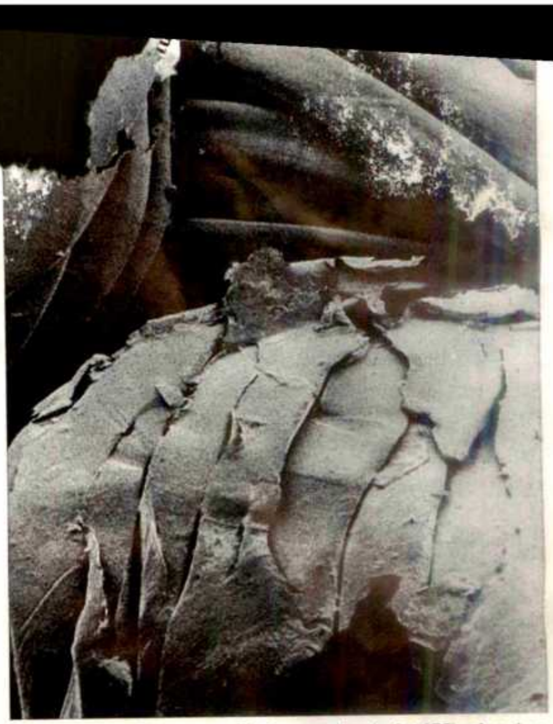

Fig. 3. Edwards's woven Teflon prosthesis (× 475), showing how the yarn has been crushed and split in the crimping process.

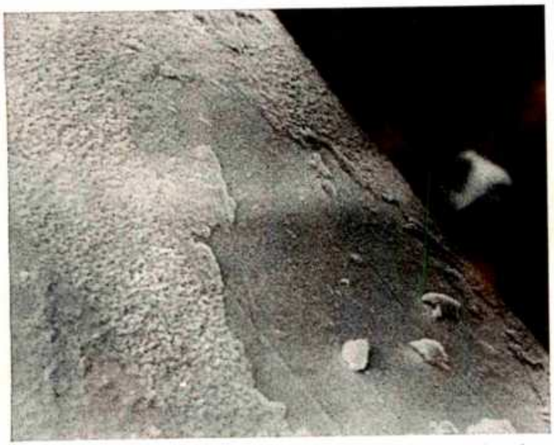

Fig. 2. Cooley double velour prosthesis (× 12 700), showing the surface of a single fibre where the 'finish' has flaked off.

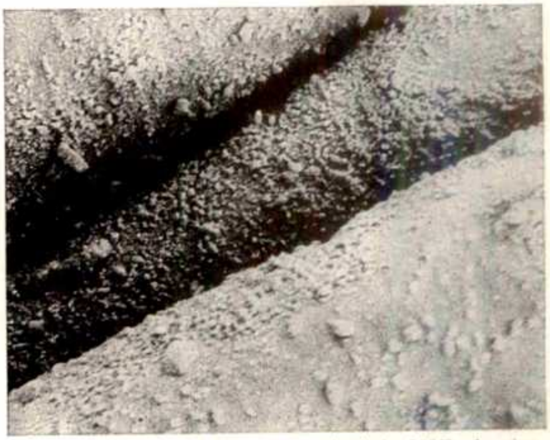

Fig. 4. Cooley knitted Dacron prosthesis (× 3800), showing the surfaces of three fibres after repeated sterilization. The granules on the surface are cyclic oligomer.

extruded. During the spinning process the fibres are passed through a tank of 'spin finish' which contains antistatic (this helps to repel particles of dust that adhere to the fibres and allows one thread to slip over another in the knitting and weaving processes). The yarn is knitted in one of two ways—warp or weft. In weft knitting a tube is knitted in a spiral using only one or two yarns; warp knitting is a more complicated process, a series of tubes being knitted at the same time. Inevitably oil from the machinery is absorbed into the yarn during these processes. The tubes are then bleached, scoured and washed in various wetting agents and solvents to remove the spin finish, oil and other impurities. The tubes are crimped by placing them over a mandrel, a strong thread is wound round in a spiral and then heat-set in that position. Further finishes may be applied to make the graft easier to handle or to make it waterproof. Some grafts, the knitted Teflon and the Cooley double velour, still had traces of a finish on them and the woven Teflon was damaged extensively where the crimps had been set during the manufacturing process. Woven Teflon prostheses are virtually impervious and are seldom associated with aneurysm formation, so

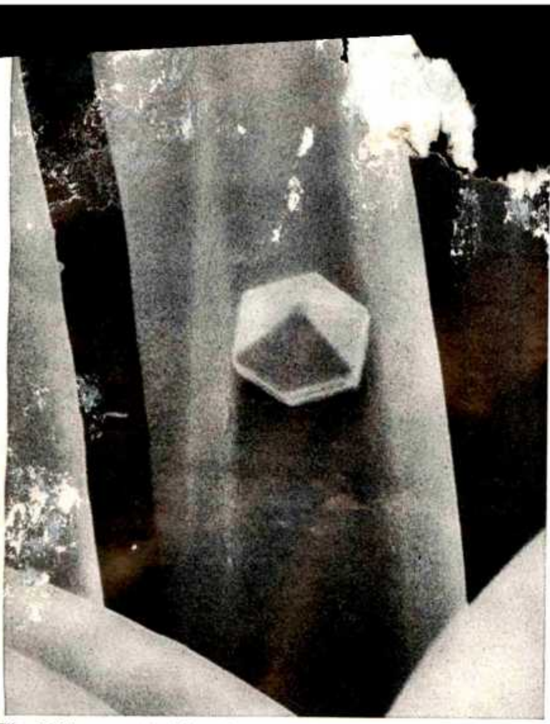

Fig. 5. Sauvage double velour prosthesis (× 4700), showing a single cyclic oligomer crystal on the surface of a fibre.

the damaged fibres do not seem to alter their strength materially. We were unable to identify precisely what 'finish' remained on the yarn of the Cooley velour graft but it appears to be a water-repellent. This suggests that either the scouring processes are not thorough enough or that a finish is applied after the washing process to modify the properties of the fabric. If the latter is the case then by the time the prosthesis reaches the consumer considerable amounts of the finish have flaked off. The Teflon prostheses, both knitted and woven, were interesting in that tiny strands of Teflon were seen to be stretched between individual fibres. These microscopic strands were only seen at high magnification and presumably formed after the fabric was woven.

ron showed remarkable ization. A coating of crystals of was seen over the fibres of the yarn, a ch became increasingly thick with each sequent resterilization. It seems likely that the polymers which make up the fibres break up into smaller chains, some containing only a few monomer units. These monomers may then crystallize at the surface. A coating of such crystals may have deleterious effects, it may interfere with the adherence of the pseudointima or the crystals may be washed away. Our preliminary investigations show that cyclic oligomer crystals can cause haemolysis but there is no apparent effect on the coagulation of blood.

Of all the prostheses, only Gore-Tex was permanently damaged by clamping, but the manufacturers do warn that the material should not be handled by instruments or clamped tightly. When the material was clamped the fibres were fused together, obliterating all the intervening spaces. This would prevent infiltration of fibroblasts and may affect the formation of a satisfactory intima. The other prostheses were not damaged to the same extent, but again the interstices between fibres were altered and the consequences may be the same.

The changes produced by clamping can be avoided with care, but those produced by resterilization cannot. Most prostheses are supplied ready for use but it is occasionally necessary for the sake of economy to resterilize a prosthesis or part of it. We were scrupulously careful to follow the manufacturers' recommendations when resterilizing the prostheses. Crystals of cyclic oligomer appeared on all Dacron fibres but were more apparent in the Cooley knitted Dacron graft.

We started this work as a preliminary to measuring the porosity of various prostheses and we were surprised to find that the quality control applied to some of the grafts we examined was less stringent than we might have hoped. It seems that the process of manufacture can result in permanent damage to arterial prostheses and introduce chemicals into the body, the effects of which are as yet unknown.

Reference

ALLEN T. D. and SIMMENS S. C. (1976) Conversion of vacuum coating units for sputter coating. *Micron* 7, 141–144.

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Assessment of carot[illegible] using pulse wave transit time

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SUMMARY

A prospective study has been undertaken on 24 patients to establish the relationship between the degree of internal carotid artery stenosis, as estimated by arteriography, and the pulse wave transit time in the carotid artery. The technique involves the simultaneous [illegible] of two continuous wave Doppler velocimeters, one on the carotid and one on the supraorbital artery, to measure the flow waves and hence deduce the pulse wave transit times. The measured transit times varied from 17 to 124 ms with a beat-to-beat variation of 11 per cent.

The absolute transit time in any segment correlated moderately well with the estimated degree of stenosis ($r = 0{\cdot}68$, $P < 0{\cdot}001$). However, normalization of the transit times, to correct for the effects of blood pressure and age, produced an improved correlation between the variables ($r = 0{\cdot}8$, $P < 0{\cdot}001$). Normalization was achieved by dividing the common carotid to supraorbital transit time by the shortest transit time found between the common carotid and either the superficial temporal or brachial arteries.

Significant differences in the normalized transit times were found between arteries that were diametrically stenosed by more than 50 per cent, by between 21 and 50 per cent and by 20 per cent or below. It is concluded that pulse wave transit time measurement can provide a simple and reproducible non-invasive technique for the diagnosis of varying degrees of carotid artery stenosis.

THE annual reports of the Registrar-General for England and Wales indicate that the overall mortality from cerebrovascular disease is increasing and currently accounts for 13 per cent of all deaths. The death rate has risen from 1226 per million population per year in 1965 to 1525 per million population per year in 1975, the incidence being 50 per cent greater in women than in men.

Many patients with cerebrovascular disease present with transient ischaemic attacks (TIAs) and it has been shown that approximately 30 per cent of these patients, if left untreated, are likely to develop a stroke within 5 years (Fields et al., 1970). Patients who present with an asymptomatic carotid bruit pose a further problem. Javid et al. (1970) have shown that in 34 per cent of patients with an asymptomatic carotid bruit there is progression of the degree of stenosis by more than 25 per cent per year. It has been suggested that if patients with asymptomatic bruit are left untreated 46 per cent will develop transient ischaemia or frank stroke within 10years (Thompson et al., 1976). Recent studies (Kartchner and McRae, 1977) have indicated that, of those patients with TIAs, those who are most likely to have a stroke are the ones with a rapidly increasing carotid stenosis.

Surgically accessible extracranial carotid artery disease has been found in approximately 35 per cent of all cases of ischaemic cerebrovascular disease (Fields et al., 1968). The recent improvement in the understanding of the physiology of the cerebral circulation, combined with increased surgical and anaesthetic expertise, has resulted in minimal operative mortality and morbidity in carotid endarterectomy. Thus, many patients with transient ischaemic attacks or increasing carotid stenosis are now treated surgically to prevent strokes.

Since the first recorded case of successful carotid artery reconstruction for recurrent cerebrovascular symptoms (Eastcott et al., 1954), there has been increasing interest in carotid artery surgery. Until recently, the only way of assessing carotid artery disease has been carotid arteriography, by direct puncture or via the aortic arch. However, [illegible] arteriography is expensive, requires very expert radiology and is potentially hazardous. Reported mortality and morbidity is 0·7 and 0·5 per cent respectively (Hass et al., 1968).

Any non-invasive technique which could approach the accuracy of arteriography would offer great advantages, allowing the monitoring of patients with asymptomatic bruits and selecting patients with TIAs into those with increasing carotid stenosis, i.e. those who are at greatest risk from stroke and would therefore benefit most from prophylactic surgery.

Many non-invasive techniques for diagnosing carotid artery stenosis have been reported in the literature. The first technique, attributed to Brochenbrough (1964), is based on detecting the direction of flow in the supraorbital artery using an ultrasonic velocimeter. This simple test has been found, however, to be only 60 per cent accurate in diagnosing lesions of greater than 75 per cent stenosis. Other developments have included pneumo-oculoplethysmography (Gee et al., 1974, 1976), phonoangiography (Kartchner et al., 1973; Duncan et al., 1975), thermography (Wood et al., 1965), rapid sequence scintiphotography (Maynard et al., 1969), ocular plethysmodynamometry (Sand et al., 1975) and fluid-filled oculoplethysmography (Kartchner et al., 1973). Of these techniques, fluid-filled oculoplethysmography has been reported as the most accurate (Gross et al., 1977), being approximately 80 per cent accurate at diagnosing haemodynamically significant stenoses.

The major drawbacks of many of these methods are that they are costly in terms of both equipment and staff, and in some cases are distinctly unpleasant for the patients. Accordingly a great deal of attention has been focused on the application of Doppler ultrasound (Brinker et al., 1968; Grossman and Wood, 1968; Maroon et al., 1969; Wise et al., 1971; Machleder, 1973; Mol and Rijcken, 1974; Baskett et al., 1977). All of these techniques offer the potential for investigating repeatedly, safely and atraumatically the patency of a specific vessel segment. In practice, however, none of the available ultrasonic techniques has been found to be capable of reliably detecting diametral stenoses of less than 60 per cent. The application of ultrasonic velocimetry to the diagnosis

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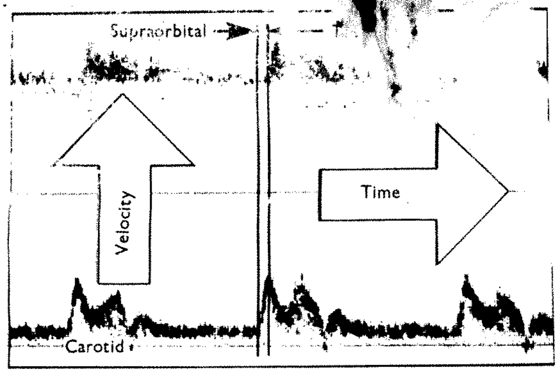

Fig. 1. Typical two-channel print-out of carotid and supraorbital sonograms.

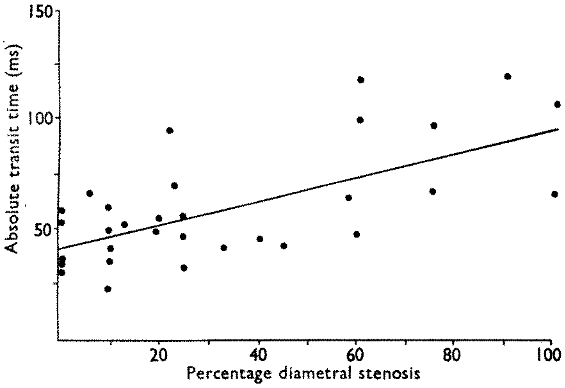

Fig. 2. Absolute transit time against percentage stenosis of the internal carotid artery.

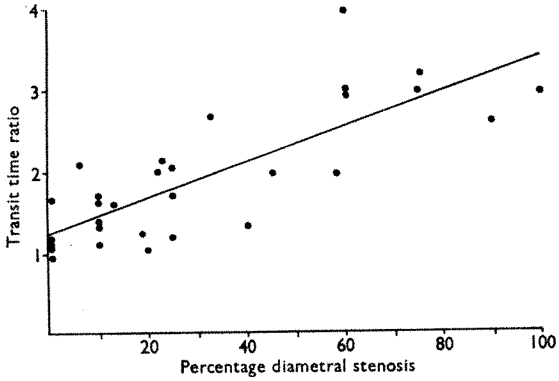

Fig. 3. Transit time ratio against percentage stenosis of the internal carotid artery.

of disease in the leg has indicated that the measurement of pulse transit times can be a sensitive indicator of arterial occlusion especially when normalized to compensate for changes in blood pressure and age (Cotton et al., 1976). This present work is the result of an attempt to apply this finding to the diagnosis of carotid artery disease.

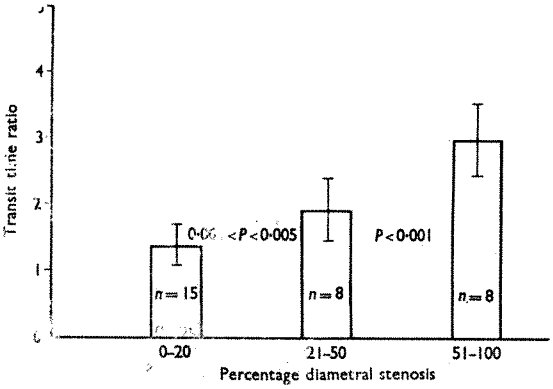

Fig. 4. Transit time ratio in the three groups of patients.

Patients and methods

Twenty-four patients (15 men and 9 women) who were to undergo carotid arteriography, mainly for symptoms of transient cerebral ischaemia, were assessed by the technique. The ages of the patients ranged from 34 to 77 years with a mean of 59 years. All patients had both carotid arteries studied, and the results were recorded and processed before arteriography was undertaken.

Arteriography

Most of the patients had direct puncture carotid arteriograms, with biplanar views of the carotid bifurcation and the whole of the extra- and intracranial arteries. The carotid arteriograms were assessed blind by three independent observers all experienced in reporting carotid arteriograms. Each observer individually assessed the percentage of narrowing of the internal carotid artery by taking the transverse diameter of the narrowest lesion and comparing this to the nearest adjacent normal calibre carotid artery. These figures were then averaged to produce a mean figure for further correlation.

Where there was significant disagreement in the interpretation of the X-rays, particularly when the quality of the X-ray was so poor that it was felt unreasonable to compromise, then the patients concerned were excluded.

Methods

The pulse wave velocity in the internal carotid artery system was assessed by measuring the time taken for the pulse wave to travel to the supraorbital artery from the common carotid artery. The supraorbital artery is a major branch of the ophthalmic artery, itself the first major branch of the internal carotid artery.

To assess the external carotid artery system for comparison, the time taken for the pulse wave to travel to the frontal branch of the external carotid artery from the common carotid artery was measured. The frontal artery is a branch of the superficial temporal artery, which is itself a major branch of the external carotid. To obtain a normalizing factor to allow for the influence of systemic blood pressure and the effects of age, the pulse wave transit time between the common carotid artery and the brachial artery was also measured on both sides. This arterial segment was chosen on the basis that it was essentially of a similar length to those under primary investigation. In our experience it is quite common to have unilateral or bilateral external carotid artery disease or subclavian artery disease, but it is extremely rare to have both external carotids and both subclavians diseased in the same patient. We therefore chose the shortest transit time from these segments as being the normal for the patient.

All pulse wave transit times were measured using two continuous wave ultrasonic Doppler velocimeters. A 5-MHz system was used on the common carotid and a 10-MHz system on the peripheral vessels. In order to standardize the probe position in relation to the common carotid, the proximal end of the pencil probe was rested on the medial end of the clavicle. The supraorbital artery was insonated at the supraorbital ridge with the probe pointing away from the eye. The frontal artery was insonated at the level of the supraorbital ridge in the temporal fossa. Finally, the brachial arteries were insonated 3 cm above the medial epicondyle of the humerus. Two observers were required, one for each Doppler system.

The outputs from the Doppler velocimeters were fed to a two-channel real-time spectrum analyser (Stevens and Roberts, 1976). This analyser is of the time-compression type which does a complete spectral analysis every 10 ms between 0 and 5 kHz or between 0 and 10 kHz. The output from the analyser is fed to a fibreoptic recording oscilloscope to give a hard-copy sonogram.

The sonogram tracing correlates the Doppler shift frequency (in kHz) on the ordinate against time on the abcissa, with darkening corresponding to spectral density. Since the Doppler shift is directly proportional to the blood velocity, the sonogram trace effectively shows the velocity wave at that site in the arterial tree.

Fig. 1 shows a typical two-channel sonogram. On the lower line is the common carotid sonogram and on the upper line the supraorbital sonogram. The pulse wave transit time is measured as the time interval between the foot of the systolic upswing of the carotid sonogram and the corresponding point on the supraorbital sonogram. The illustration does not adequately illustrate the grey scale definition available from the recordings, and the spatial resolution of the transit time is better than suggested by the illustration. In practice, when both observers have obtained optimum signals from the two Doppler velocimeters the sonograms are printed out simultaneously on to the same ultraviolet-light-sensitive paper, and a minimum of ten consecutive pulses recorded.

The recordings were analysed with the aid of a Hewlett Packard desk-top calculator interfaced to a digitizing platen, the spatial resolution of which was 0·25 mm. Supraorbital sonograms are often difficult to interpret and the restrictions imposed by the sonogram analyser meant that the overall temporal resolution of the measurements was ±5 ms. Each patient's transit times were measured by three independent observers. Each individual pulse was measured three times and ten pulses were measured for each arterial segment. An average was then taken of all the transit times to obtain mean values for each segment. Thus at the end of the investigation each patient ended up with six mean transit times—two supraorbital, two frontal and two brachial.

Results

A total of 40 carotid arteriograms was performed. Of these, 9 were found to be unsatisfactory in that the degree of stenosis could not be determined. There were no exclusions on the basis of inadequate ultrasonic data. The variability of the transit time measurement obtained from any segment was found to be less than 11 per cent, and this figure includes both the intra-beat variation, the intra-observer variation and the variability of each repeated observation. The mean values of transit times varied from 17 to 124 ms.

Fig. 2 shows the results of plotting the common carotid to supraorbital transit time against the percentage diametral stenosis in the internal carotid. The correlation is only moderate ($r = 0{\cdot}68$, $P < 0{\cdot}001$).

In order to compensate for the effects of age, blood pressure and any bilateral carotid disease on a measured absolute transit time, the supraorbital transit times were divided by the shortest or either the frontal or brachial transit times for each patient for the reasons discussed previously. The transit time ratios were then plotted against the percentage diametral stenosis and the result is shown in *Fig*. 3. Here the correlation coefficient is better ($r = 0{\cdot}8$, $P < 0{\cdot}001$).

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2. Minimal disease: Those with a diam 20 per cent or less (which is the degree to be expected of a 'normal' patient of an age to those in our study [Rutherford et al., 1977]).

3. Moderate disease: The remainder, i.e. those with a diametral stenosis between 21 and 50 per cent.

Fig. 4 shows the results of this classification. On the vertical axis is the normalized transit time ratio and on the horizontal axis are the three groups of patients. The mean transit time ratio for stenoses of 51 per cent or greater was $2{\cdot}98 \pm 0{\cdot}56$, that for stenoses between 21 and 50 per cent was $1{\cdot}90 \pm 0{\cdot}47$ and that for stenoses of 20 per cent or less was $1{\cdot}35 \pm 0{\cdot}32$. Assessment with the Student t test reveals a significant difference between the moderately and minimally diseased groups ($0{\cdot}001 < P < 0{\cdot}005$) and between the moderately and severely diseased groups ($P < 0{\cdot}001$).

Discussion

There are several possible explanations of the increasing transit time with stenosis. The foot-to-foot transit time gives an unambiguous measure of pulse wave velocity only where the velocity wave form does not change as it progresses along the arterial system. However, in practice it changes in response to reflections, branching and tapering of the arterial tree. In addition, high frequency components of the wave are attenuated by stenosis (Womersley, 1958). Since the high frequency components tend to travel faster than the low frequency components, their attenuation leads to an apparent increase in the transit time.

As the distensibility of arteries becomes less, as it does with ageing, so the pulse wave velocity will increase. Furthermore, vessels become less distensible as they are stretched. If the pressure in an artery increases, there is a decrease in distensibility and a corresponding increase in pulse wave velocity. Conversely, if the pressure in an artery decreases, then distensibility increases and there is a fall in pulse wave velocity. Carotid arteries have been shown to be among the most distensible arteries in the body (Caro et al., 1978) and pressure drops (caused by local stenoses) of the order of 80 mmHg have been found in the carotids during carotid endarterectomy (Roberts, 1978), for example, from 130 mmHg in the common carotid to 50 mmHg in the internal carotid. This drop would lead to a tripling of the transit time in the artery distal to the stenosis (King et al., 1972).

All these factors help to explain the apparent decrease in pulse wave velocity with increasing carotid artery stenosis and explain why lesser degrees of stenosis are detectable by this technique compared with any other non-invasive technique.

We have demonstrated that there is a prolongation of both the absolute transit time and the transit time ratio with increasing internal carotid artery stenosis, but the work is of little value unless the measurement can be used predictively. In this respect the prognostic value of a transit time ratio of greater than 2·75 is approximately 85 per cent correct in predicting ut la e in pr sten of compares y favou ly wi asive techniques.

Conclusion

We have demonstrated that the transit time ratio can differentiate between minimal, moderate and severe disease. We feel that this technique is particularly useful as it only takes a few minutes to perform, it can be performed by technical staff after minimal training and it is completely non-invasive.

This technique can be used in a variety of clinical problems—evaluation of the asymptomatic bruit, assessment of bilateral stenosis to help decide which side to operate on first, monitoring of patients post-operatively both immediately and in the long term, evaluation of ambiguous neurological or cerebrovascular symptoms, screening of carotid arteries before major abdominal vascular procedures and for screening young patients with evidence of other arterial disease. Further studies are now being undertaken to evaluate this technique for monitoring patients both in the immediate postoperative period and on a long term basis.

We conclude that measuring the pulse transit time ratio is a valuable non-invasive technique for diagnosing and monitoring patients with extracranial carotid artery disease.

Acknowledgements

The authors are indebted to the South-East Thames Regional Health Authority for funding this investigation and to Mrs D. J. Berlyn for her expert secretarial assistance.

References

BASKETT J. J., BEASLEY M. G., MURPHY G. J. et al. (1977) Screening for carotid junction disease by spectral analysis of Doppler signals. *Cardiovasc. Res.* **11**, 147–155.

BRINKER R. A., LANDISS D. J. and CROLEY T. F. (1968) Detection of carotid artery bifurcation stenosis by Doppler ultrasound. *J. Neurosurg.* **29**, 143–148.

BROCKENBROUGH E. C. (1964) *Screening for the Prevention of Stroke.* Seattle, Parks Electronics.

CARO C. G., PEDLEY T. J., SCHROTER R. C. et al. (1978) *The Mechanics of the Circulation.* London, Oxford University Press.

COTTON L. T., ROBERTS V. C., SAINZ A. et al. (1976) Doppler shift spectra in the assessment of peripheral arteries. *J. Physiol (Lond.)* **266**, 17P.

DEWEESE J. A., MAY A. G. and LIPCHIK E. O. (1970) Anatomic and haemodynamic correlations in carotid artery stenosis. *Stroke* **1**, 149–157.

DUNCAN G. W., GRUBER J. O., DEWEY F. C. et al. (1975) Evaluation of carotid stenosis by phonoangiography. *N. Engl. J. Med.* **293**, 1124–1128.

EASTCOTT H. H. G., PICKERING G. W. and ROB C. G. (1954) Reconstruction of the internal carotid artery in patients with intermittent attacks of hemiplegia. *Lancet* **2**, 994–996.

FIELDS W. S., NORTH R. R., HASS W. K. et al. (1968) Joint study of extracranial arterial occlusion as a cause of stroke (I). *JAMA* **203**, 955–960.

s W. S., MASLENIKOV V., MEYER J. S. et al. (1970) Joint study of extracranial arterial occlusion (V). *JAMA* **211**, 1993–2003.

W., OLLER D. W. and WYLIE E. J. (1976) Non-invasive diagnosis of carotid occlusion by ocular pneumoplethysmography. *Stroke* **7**, 18–21.

W., SMITH C. A., HINSEN C. E. et al. (1974) Ocular pneumoplethysmography in carotid artery disease. *Med. Instrum.* **8**, 244–248.

s W. S., VERTA M. J., VAN-BELLEN B. et al. (1977) Comparison of non-invasive diagnosis techniques in carotid artery occlusive disease. *Surgery* **82**, 271–278.

IAN B. L. and WOOD E. H. (1968) Evaluation of cerebrovascular disease utilizing a transcutaneous Doppler technique. *Radiology* **90**, 586.

HASS W. K., FIELDS W. S. and BAUER R. B. (1968) Joint study of extracranial arterial occlusion (II). *JAMA* **203**, 961–968.

JAVID H., OSTERMILLER W. E., HENGESH J. W. et al. (1970) Natural history of carotid bifurcation atheroma. *Surgery* **67**, 80.

KARTCHNER M. M., MCRAE L. P. and MORRISON F. D. (1973) Noninvasive detection of evaluation of carotid occlusive disease. *Arch. Surg.* **106**, 528–535.

KARTCHNER M. M. and MCRAE L. P. (1977) Noninvasive evaluation and management of the 'asymptomatic' bruit. *Surgery* **82**, 840–847.

KING D., COGLAN B., GOSLING R. et al. (1972) Transcutaneous measurement of pulse wave velocity and mean blood pressure in man. In: ROBERTS V. C. (ed.) *Blood Flow Measurement.* Tunbridge Wells, Pitman Medical, pp. 40–43.

MACHLEDER H. I. (1973) Evaluation of patients with cerebrovascular disease using the Doppler ophthalmic test. *Angiology* **24**, 374–381.

MAROON J. C., PIERONI D. W. and CAMPBELL R. L. (1969) Ophthalmosonometry—an ultrasonic method for assessing carotid blood flow. *J. Neurosurg.* **30**, 238–246.

MAYNARD C. D., WITCOFSKI R. L. and JANEWAY R. (1969) Radioisotope arteriography: as an adjunct to the brain scan. *Radiology* **92**, 908–912.

MOL J. M. F. and RIJCKEN W. J. (1974) Doppler haemotachographic investigation in cerebral circulation disturbances. In: RENEMAN R. (ed.) *Cardiovascular Application of Ultrasound.* Amsterdam, North-Holland, pp. 305–314.

ROBERTS V. C. (1978) Unpublished observations.

RUTHERFORD R. D., HIATT W. R. and KREUTZER E. W. (1977) The use of velocity wave form analysis in the diagnosis of carotid artery occlusive disease. *Surgery* **82**, 695–702.

SAND B. J., WILEY F. B., FREEMAN L. W. et al. (1975) Ophthalmic arterial blood pressures measured by ocular plethysmodynamography. *Arch. Surg.* **110**, 813–818.

STEVENS A. L. and ROBERTS V. C. (1976) On-line signal processing of CW Doppler shifted ultrasound. In: *Proceedings XIth International Conference on Medical and Biological Engineering.* Ottawa, National Research Council of Canada, pp. 160–161.

THOMPSON J. E., RATMAN R. D. and PERSON A. V. (1976) Management of asymptomatic carotid bruit. *Ann. Surg.* **42**, 77–80.

WISE G., BROCKENBROUGH E. C. and MARTY R. (1971) The detection of carotid artery obstruction: a correlation with arteriography. *Stroke* **2**, 105–113.

WOMERSLEY J. R. (1958) Oscillatory flow in arteries. Reflections of the pulse wave at junction and rigid inserts. *Phys. Med. Biol.* **2**, 313–323.

WOOD E. H., HILL R. and HEYMAN A. (1965) Diagnostic value of thermography in extracranial carotid occlusive disease. *Trans. Am. Neurol. Assoc.* **90**, 124–127.

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Radiological assessment of nipple-valve insufficiency in Kock's continent reservoir ileostomy

C.-G. STANDERTSKJÖLD-NORDENSTAM, [illegible] PALMU AND A. SIVULA*

SUMMARY

In a series of 51 continent reservoir ileostomies nipple-valve insufficiency developed in 15 patients who were examined radiographically to find the cause for the loss of continency. The radiological diagnosis was confirmed at reoperation. The causes for nipple-valve insufficiency were a total or partial disappearance of the nipple-valve by sliding of the invaginate (7 cases) and dislocation of an undamaged nipple out of the reservoir (8 cases). In these groups the radiological diagnosis was compatible with the operative findings in all but one case. At reoperation a fistula in the nipple-valve was found in 3 cases, but in no instance had this been diagnosed radiologically. A correct preoperative diagnosis is valuable, especially in cases of dislocation, where a danger exists that the real mechanism of valve insufficiency may remain obscure at operation.

NIPPLE-VALVE insufficiency is a recognized complication of Kock's continent reservoir ileostomy (Kock, 1976). In a previous paper two of the present authors reported results from 51 operations and nipple-valve insufficiency developed in 15 of these (Palmu and Sivula, 1978). At reoperation two different mechanisms causing insufficiency were found: disappearance of the nipple-valve by sliding of the invaginate (7 cases) and dislocation of an undamaged nipple out of the reservoir (8 cases). Furthermore, a fistula at the base of the nipple was found in connection with partial sliding in 1 patient and in connection with dislocation in 2 patients. Before reoperation the ileostomy reservoir and nipple-valve were examined radiologically. During the course of the series a specific radiological examination technique was developed to find criteria on which a preoperative diagnosis of the mechanism causing nipple-valve insufficiency could be made.

Patients and methods

In 1972–7 a continent reservoir ileostomy was created in 51 patients. Of these, 15 developed nipple-valve insufficiency, most often within 3–6 months of operation. The nipple-valve insufficiency manifested as difficulties in catheterization of the reservoir and spontaneous leakage of gas and bowel contents. In an attempt to elucidate the reasons for these disturbances radiological examinations were performed preoperatively and the results were compared with the findings at reoperation.

Radiological technique

The procedure is performed as a double-contrast study in order to visualize the nipple-valve properly.

1. The ileostomy is catheterized with the same type of large bore (10 mm outer diameter), rather stiff catheter that the patient uses for emptying the reservoir (ileostomy catheter, Medena M 8730, Astra-Sjuco AB). The reservoir is then filled, through the catheter, with ordinary barium contrast medium until the distal end of the ileum is full.

2. The barium is then emptied through the same catheter and air is insufflated.

3. Pictures are taken with the catheter still in the valve in (1) the anteroposterior position and (2) in the left anterior oblique projection, tangentially to the valve.

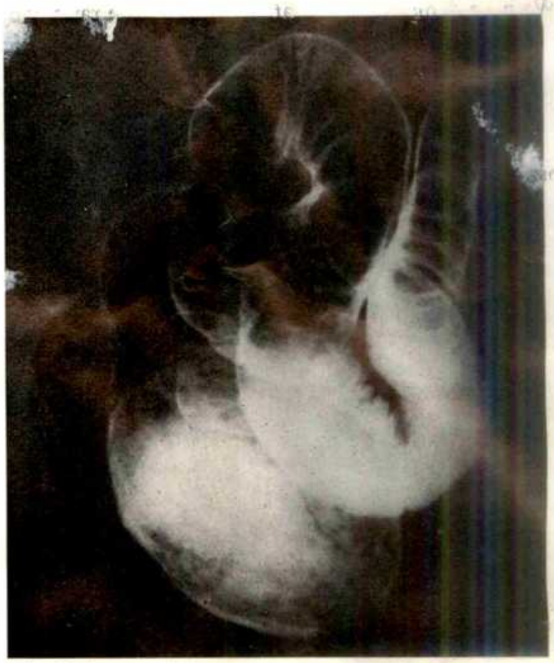

Fig. 1. The normal ileostomy reservoir seen in the anteroposterior view. The nipple-valve is not adequately demonstrated in this projection.

4. More air may be insufflated and the catheter is withdrawn. The tangential pictures are repeated (1) with the patient at rest and (2) with the patient straining.

Results

Radiological findings

Whilst at rest and also when straining, the normal nipple-valve protruded symmetrically 3–5 cm into the internal ileostomy pouch and retained its size and shape both with the catheter introduced and without the catheter (*Figs.* 1 and 2).

When sliding damage to the nipple-valve was present, catheterization was often difficult. When it succeeded no nipple-valve could be seen in the ileostomy pouch. Without the catheter the efferent channel often appeared tortuous and elongated as a result of malpositioning of the bowel which had become loosened from the invaginated nipple by sliding. In partial sliding a short and/or asymmetrical nipple-valve was seen (*Figs.* 3 and 4).

Dislocation of the nipple was characterized by a normal nipple-valve at catheterization, but disappearance of the nipple when the catheter was withdrawn

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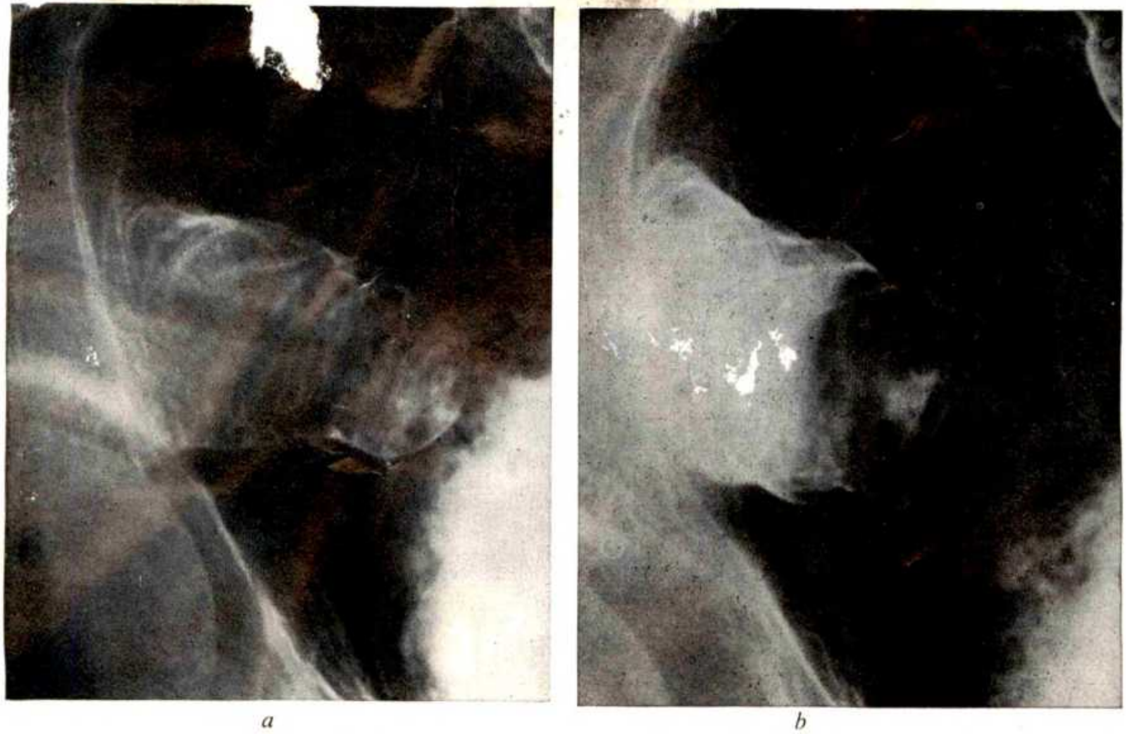

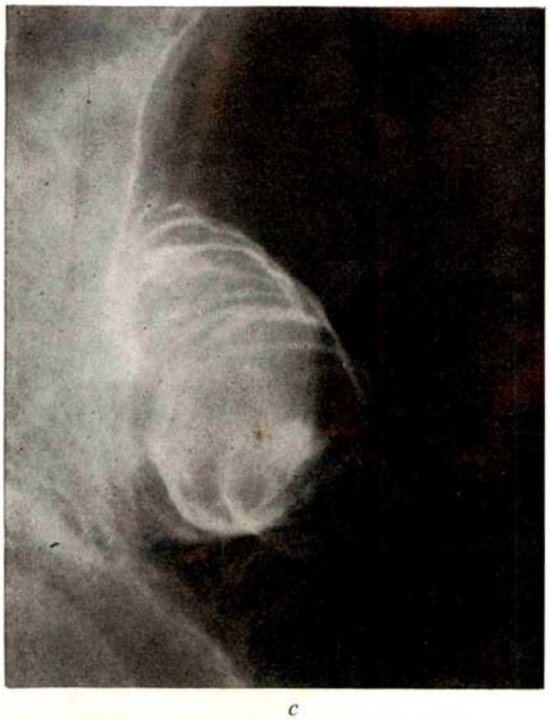

Fig. 2. A normal nipple–valve (left anterior oblique projection) (*a*) with the catheter inserted through the valve, (*b*) without the catheter and the patient at rest and (*c*) without the catheter and with the patient straining. The nipple–valve retains its shape and position throughout the examination.

Table I: COMPARISON OF RESULTS OF PREOPERATIVE RADIOGRAPHY OF THE NIPPLE–VALVE AND OPERATIVE FINDINGS

Case	Radiography	Operation
1	Sliding*	Sliding, fistula
2	Sliding*	Sliding
3	Dislocation	Dislocation, fistula
4	Dislocation	Dislocation
5	Sliding	Sliding
6	Dislocation	Dislocation
7	Dislocation	Dislocation
8	Dislocation	Sliding
9	Sliding	Sliding
10	Dislocation	Dislocation, fistula
11	Dislocation	Dislocation
12	Sliding	Sliding
13	Sliding	Sliding
14	Dislocation*	Dislocation
15	Dislocation	Dislocation

* Radiographic differential diagnosis between dislocation and sliding was more difficult than usual because the catheter could not be properly introduced through the nipple–valve.

and the patient strained. The nipple was often easily repositioned with the catheter (*Fig*. 5).

No fistulas could be identified radiologically.

Operative findings

When sliding of the invaginate had occurred, there was no nipple to be found in the opened reservoir at reoperation. It had disappeared by loosening of the invaginate and the loosened part of the bowel had escaped from the reservoir forming a tortuous and elongated outlet segment. In some cases the sliding was partial and there was a short stub or a semicircular fold in the reservoir, both remnants of the previous nipple–valve.

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[illegible]echnique used in patients in this series [illegible]ted by practical considerations. Simple [illegible] [illegible]re of a child's colostomy is difficult in that there [illegible]ually much more oedema and hypertrophy of the [illegible]el mucosa at the site of the colostomy than in [illegible]ts: resection of bowel either side of the colostomy [illegible]s much more satisfactory material to suture. The [illegible]tively thin abdominal wall in children and the [illegible]ence of a skin, or skin and muscle, bridge makes [illegible]aperitoneal closure a difficult or even impossible [illegible]position. Finally, a single-layer anastomosis was [illegible]d in infants because it was thought that a standard t[illegible]-layer closure would unduly compromise the e[illegible]ctive lumen of the anastomosis.

[illegible] is, of course, impossible to make direct comparison between the results of these techniques applied to children and the results of various techniques reported in adult practice, but we feel that our results are acceptable in terms of the incidence of major complications. It is doubtful whether the incidence of such complications could be much reduced, except by emphasizing the importance of excluding distal obstruction, Hirschsprung's disease in particular, before closing a child's colostomy, even though such an obstruction need not necessarily lead to anastomotic breakdown. Possibly more of the faecal fistulas [illegible] conservatively, [illegible] peritonitis, re[illegible] probably the more [illegible]

[illegible]ion, this being [illegible]rted series of [illegible]son why this [illegible]d information [illegible] appears that [illegible]ration reduces [illegible] Of the factors [illegible]provement (i.e. [illegible]n and different [illegible] use of metro[illegible] [illegible] to reduce the incidence [illegible] in colonic surgery (Willis et [illegible] [illegible]portant.

References

FINCH D. R. A. (1976) The [illegible]ults of colostomy closure. *Br. J. Surg.* 63, 397–399.

KNOX A. J. S., BIRKETT F. D. H. and COLLINS C. D. (1971) Closure of colostomy. *Br. J. Surg.* **58**, 669–672.

THOMSON P. S. and HAWLEY P. R. (1972) Results of closure of loop transverse colostomies. *Br. Med. J.* **3**, 459–462.

WHEELER M. H. and BARKER J. (1977) Closure of colostomy—a safe procedure? *Dis. Colon Rectum* **20**, 29–32.

WILLIS A. T., FERGUSON I. R., JONES P. W. et al. (1977) Metronidazole in prevention and treatment of Bacteroides infections in elective colonic surgery. *Br. Med. J.* **1**, 607–610.

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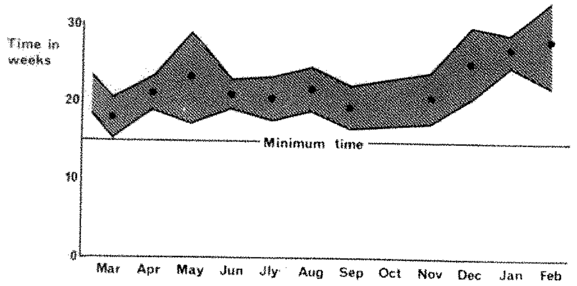

Time from acceptance to publication of articles in the *British Journal of Surgery* (mean ± 1 s.d.).

Closure [illegible] id en

A. M. K. RIC[illegible] [illegible] MAN*

SUMMARY

A retrospective sur[illegible] closures in infants [illegible] operative technique consisted [illegible] anastomosis, usually as a sin[illegible] toneal closure. Faecal fistula [illegible] there were other major comp[illegible] Wound infection occurred in 4[illegible] use of a more aggressive bowel pre[illegible] uced the incidence of this complication.

In adult patients closure of a temporary colostomy is a common surgical procedure, and, outside centres specializing in colorectal surgery (Thomson and Hawley, 1972), there is a high reported incidence of major complications, such as faecal fistula (Knox et al., 1971; Wheeler and Barker, 1977) and incisional hernia (Finch, 1976). Temporary colostomy in a child is comparatively rare, Hirschsprung's disease and some types of imperforate anus being the commonest indications for the procedure. However, many colostomies are closed in centres specializing in paediatric surgery, and we present here the results from one such centre because the techniques employed differ in some respects from those generally used in adult practice.

Patients and methods

This comprises a retrospective study of 100 consecutive colostomy closures from January 1969 to May 1978. Only those cases in which a colocolic anastomosis was performed are included. There were 71 male and 29 female patients. The indication for the colostomy was imperforate anus in 47 cases, Hirschsprung's disease in 34 cases, neonatal necrotizing enterocolitis in 7 cases and miscellaneous reasons in the remaining 12 cases. Eighty-five colostomies were of the loop type brought out over a skin, or skin and muscle, bridge and 15 were split (defunctioning) colostomies. The site was the right transverse colon in 49, the left transverse colon in 4, the descending colon in 3 and the sigmoid colon in 44 instances. By virtue of the primary pathology, the series is biased towards infancy, 58 patients being under 2 years of age at the time of colostomy closure.

No bowel preparation was given before closure in 6 patients, but the remainder received some form of preparation. Before 1975 this consisted of mechanical preparation of the distal colon and chemotherapeutic preparation of the proximal colon with an oral, non-absorbable sulphonamide; this was used in 69 cases. From 1975 onwards a more radical preparation was employed, adding mechanical preparation of the proximal colon, by the use of a low residue diet and magnesium sulphate, and chemotherapy of both the proximal and distal colon with orally and stomally administered gentamicin and metronidazole; 25 patients received this preparation.

No colostomy was closed less than 3 months after formation, nor less than 1 month after a definitive procedure to deal with the primary pathology. The operative technique consisted of circumcising the colostomy and mobilizing it into the peritoneal cavity. Between 2 and 4 cm of colon were resected on either side of the colostomy and an end-to-end anastomosis performed, as a single layer of inverting silk or Dacron mattress sutures in 83 cases and as a double layer (all layers chromic catgut, seromuscular silks) in 17 cases, all over 2 years of age. The colon was returned to the peritoneal cavity and the wound closed in layers. Drains, usually placed subcutaneously rather than intraperitoneally, were employed in 72 cases.

Results

Major complications

There were no deaths in this series. Five patients developed a faecal fistula, 3 following closure of a transverse colostomy and 2, a sigmoid colostomy. A single-layer anastomosis had been used in 3 c[illegible]es ar[illegible] bowel preparation given in 4 cases. A drain [illegible] d b[illegible] used in every case. In 4 cases there was n[illegible] obv[illegible] reason for the fistula formation, but in 1 ca[illegible], w[illegible] the colostomy had been performed in the neon[illegible] period for a colonic perforation, it was closed in [illegible] presence of unsuspected Hirschsprung's disease [illegible] the resulting distal obstruction was presum[illegible] responsible for the anastomotic leak. One of [illegible] fistulas closed spontaneously, whilst another spo[illegible]taneously re-formed the colostomy. In the remai[illegible] 3 cases there were signs of local peritonitis, and it [illegible] felt advisable formally to re-establish the colostomy.

Anastomotic strictures occurred in 2 patients, 2 and 3 weeks postoperatively. At re-exploration, in both cases, small bowel was found to be densely adherent to the anastomosis, suggesting the possibility of a previous anastomotic leak.

Other forms of postoperative obstruction were encountered in 4 cases. Two were due to ileal adhesions secondary to previous surgery. Two other patients had unsuspected Hirschsprung's disease (at the time of their colostomy closure they had been erroneously diagnosed as having 'immature bowel' syndrome). When they were re-explored 2–3 weeks postoperatively, the anastomoses were intact despite the presence of gross colonic distension. (In the same respect there were a further 3 patients who ultimately proved to have residual Hirschsprung's disease following the original pullthrough procedure, but when their colostomies were closed in the presence of this residual disease, although they were distinctly constipated in the postoperative period, none showed evidence of an anastomotic leak.)

The single cases of burst abdomen and incisional hernia were both associated with a faecal fistula.

Minor complications

Wound infection: Patients were regarded as having had a wound infection if there was a record of a purulent discharge or a positive bacterial culture from the wound. Excluding the 5 cases of faecal fistula, where the term has little meaning, wound infections so defined occurred in 43 patients (45 per cent). Of the factors that might be implicated, the site of the colostomy, the age of the patient and the use of drains were immaterial, but the more recent method of bowel preparation was associated with a reduced incidence of wound infection—4 infections in 25 cases (16 per cent).

Other minor complications: Ileus was rare. Excluding the 13 cases with major complications, only 8 patients required intravenous fluids 4 or more days postoperatively. Prolonged postoperative hospital stay was common. Of the 87 cases without a major

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Melan[illegible]a [illegible] nipple [illegible]ola

D. N. PA[illegible] [illegible]IRI, [illegible]. KINNE[illegible] [illegible] RI AN[illegible]

SUMMARY

Fourteen primary mela[illegible] [illegible]ing in the nip[illegible] areola of the bre[illegible]st we[illegible] [illegible] by mastecto[illegible] axillary dissectio[illegible]. Fou[illegible] [illegible] had axillary node metastases and all [illegible] [illegible]d within 3 y[illegible] their operation, while the [illegible] [illegible]nts with no [illegible] node involvement were fre[illegible] [illegible] recurrent di[illegible] years after their operation. [illegible] [illegible]sis of clin[illegible] anatomical studies, it is sugg[illegible] [illegible]hat a [illegible] excision wi[illegible]out mastectomy i[illegible] [illegible]at for [illegible]ment of nipple and areola m[illegible].

Malignant melanoma of the breast is rare and it is doubtful if a primary melanoma of the nipple has been reliably reported (Haagensen, 1971). Because these tumours are extremely rare, and merge into the brown pigmentation of the nipple, diagnostic delay is probable. This report describes 14 cases of proved malignant melanoma of the nipple and areola.

Patients

From May 1951 to May 1971 115 patients with cutaneous melanoma of the breast were admitted to the Memorial Hospital, New York. Thirty-four of these patients were female and 81 were male. Fourteen patients had primary melanoma arising in the nipple and areola of the breast. Four of these 14 lesions were on the nipple and 10 were in the areola. Two of the patients were female, both of whom had nipple melanomas, and 12 were men. Their median age was 32 years (range 28–62 years). All patients were regularly followed up until 1978.

Results

The incidence of nipple and areola melanomas among cutaneous melanomas of the breast was 12 per cent. The main symptom was 'a mole in the breast' (11 of the 14 patients). Three patients, 2 of whom were female, complained of nipple discharge and/or bleeding. Three patients noted 'moles which had changed' while 8 patients noted the appearance of new lesions on their nipple or areola 4–11 months before their first consultation. The average delay between the patient noting the lesion and the first consultation was 8·4 months. The diagnosis was not made at the first medical examination on 5 occasions, despite the melanomas being of characteristic appearance; 2 of these 5 patients had palpable axillary nodes.

Classification of malignant melanomas by the criteria of Clark et al. (1969) was not started in this institution until 1972. However, retrospective microstaging was possible in 9 patients. Three patients had level IV melanomas, 2 of whom had axillary node metastases, while all 5 patients with less invasive lesions (level III and level I) had no involvement of the axillary lymph nodes.

Nine patients were treated by a radical mastectomy, 4 patients by a modified radical mastectomy and 1 patient underwent an extended radical mastectomy that included internal mammary node dissection in combination with the radical mastectomy. The results of treatment were mainly influenced by the presence or absence of axillary node metastases and not by the type of mastectomy. All 4 patients who had axillary node metastases succumbed to their disease within the third post-mastectomy year. Three had been treated with a radical mastectomy and 1 with a modified radical mastectomy. In contrast, all 10 patients with no metastases in the axillary nodes survived free of disease beyond the fifth postoperative year. The only patient subjected to extended radical mastectomy had no metastases in the internal mammary nodes and survived, with no evidence of recurrent disease 10 years following the operation.

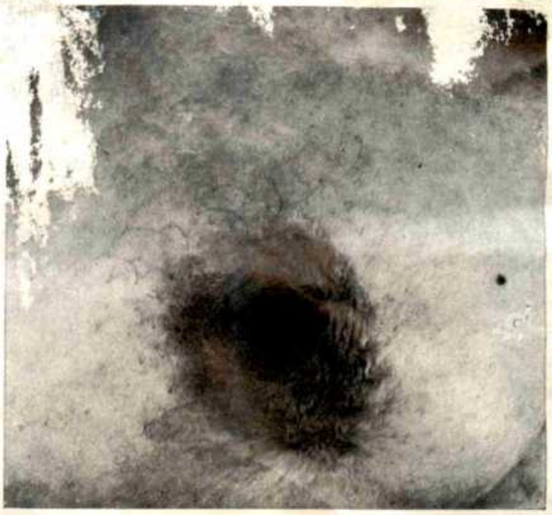

Fig. 1. Melanoma arising in the nipple.

Nipple and areola melanomas demonstrated a better prognosis and a lower incidence of nodal metastases than cutaneous breast melanomas in general. Melanomas arising in the skin of the breast gave rise to axillary metastases in 60 per cent, while only 28 per cent of areola and nipple lesions metastasized to the axillary nodes. The difference is statistically significant ($P<0{\cdot}01$, χ^2 test). Nipple melanomas had a particularly favourable course. All the 4 patients with primary nipple lesions had negative nodes, including 1 patient with a level IV tumour. All remained free of disease at the end of the follow-up period.

Discussion

Malignant melanomas of the nipple and areola are rare neoplasms (Haagensen, 1971). Surrounded by a deeply pigmented skin and covered by the clothes these lesions can escape early diagnosis. Such lesions must be differentiated from Paget's disease, seborrhoeic keratosis and benign moles; this can be accomplished only by histological examination of an excision

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[illegible] he oeles [illegible] om [illegible] de tre year. [illegible] ly pi [illegible] een [illegible] n the [illegible] e the [illegible] le and [illegible] gical excision, [illegible] that the [illegible] f distant sprea[illegible]. The inclusio[illegible] xillary [illegible]nph nodes in the dissection fo[illegible] ccepted principles of the treatment of breas[illegible] None of these patients was classified by mic[illegible] (Clark et al., 1969), but retrospective mic[illegible] was possible in 9 patients, 3 of whom had [illegible] nelanomas, with 2 of these 3 patients havin[illegible] ode metastases. Current concepts in regard [illegible] licy of elective node dissection have recently [illegible]n [illegible]sented (Fortner et al., 1977). On the basis of [illegible]is [illegible] and with accurate microstaging of the [illegible]ma, routine axillary clearance may not always [illegible]sary, as the 5 patients in this series with less [illegible] lesions had no axillary metastases, and were [illegible]ore than 5 years after their original operation.

[illegible]e lymphatic drainage of the breast was at first [illegible]sidered to be to the areola, and from the subareola [illegible]xus to the axillary lymph nodes (Grand et al., 1953). [illegible]owever, it is now accepted that the axillary nodes [illegible]ceive all lymph from the subcutaneous and the sub-[illegible]reola plexus, while the deep parenchymal ducts [illegible]irect the lymph from the mammary glands to the [illegible]xillary and internal mammary lymph nodes (Turner-Warwick, 1959; Halsell et al., 1965). It is probable that there is no communication between the subcutaneous lymphatics and those in the breast; thus,

[illegible]d for a mast[illegible] [illegible]ast skin is r[illegible] [illegible] patients in [illegible] [illegible]aries were [illegible] [illegible]oination w[illegible] [illegible] was [illegible] h [illegible]

[illegible] d that [illegible] micr[illegible] wide [illegible] exc[illegible] section would [illegible] d in agree[illegible]

CLARK W. H., [illegible] et al. (1969) [illegible] histogenesis and biologic behaviour of primary human malignant melanoma of the skin. *Cancer Res.* **29**, 705–727.

FORTNER J. G., WOODRUFF J., SCHOTTENFELD D. et al. (1977) Biostatistical basis of elective node dissection for malignant melanoma. *Ann. Surg.* **186**, 101–103.

GRAND R. N., TABAK E. J. and ADAIR E. F. (1953) The surgical significance of the subareola lymph plexus in cancer of the breast. *Surgery* **33**, 71–75.

HAAGENSEN C. D. (1971) *Diseases of the Breast.* Philadelphia, Saunders.

HALSELL J. T., SMITH J. R., BENTLAGE C. R. et al. (1965) Lymphatic drainage of the breast demonstrated by vital dye staining and radiography. *Ann. Surg.* **162**, 221–226.

TURNER-WARWICK R. T. (1959) The lymphatics of the breast. *Br. J. Surg.* **46**, 574–582.

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[illegible] *Thi*[illegible] *were* [illegible] *ears.* [illegible] *ied* [illegible] *espon*[illegible] *ent.* [illegible] *13 e*[illegible]

[illegible] treat[illegible] is [illegible] effe[illegible]ve treatment [illegible] (Landes and Leonhardt, 1967). Sclerotherapy was first used in [illegible] thirteenth century (Landes and Leonhardt, 1967) but has largely been abandoned, probably on poor evidence (*British Medical Journal*, 1973). Maloney's (1975) recent report demonstrated that sclerotherapy could be an effective form of treatment for hydrocoeles and epididymal cysts. This paper reports the results of a prospective study of sclerotherapy undertaken in Leicester.

Patients and methods

Patients

Fifty-six patients over the age of 40 with single or bilateral hydrocoeles or epididymal cysts and without an ipsilateral inguinal hernia were accepted for treatment between January 1976 and July 1977. Eleven were eventually excluded; 6 of them required surgery (4 because of a bloodstained tap and 2 because the swelling did not transilluminate) and 5 failed to complete follow-up (3 failed to attend and 2 died of unrelated causes).

Method

The scrotum was transilluminated to confirm the diagnosis and locate the testis and an 18-gauge Medicut was inserted into the upper border of the hydrocoele or cyst under local anaesthesia. A Medicut was used because a plastic cannula is less likely to traumatize the sac lining and is unlikely to slip out when aspirating fluid or injecting sclerosant. The fluid was fully aspirated using a 50-ml syringe and the volume recorded, after which the testicle was carefully palpated. The sclerosant used in this study was 2½ per cent phenol in water. The volume inserted depended on the volume of aspirate. Five millilitres were used in a sac containing up to 50 ml of fluid, 10 ml for a sac containing 51–200 ml, 15 ml for a sac containing 201–400 ml of fluid and 20 ml of 2½ per cent phenol for a sac containing more than 401 ml of fluid. To ensure complete emptying of the sac sclerosant fluid was swilled in and out before the chosen volume of sclerosant was inserted.

Patients were warned that some fluid might reaccumulate and they were seen at 6-weekly intervals when the scrotum was again aspirated and injected as before, unless (*a*) the aspirate was darker than on the first visit or (*b*) the fluid volume was much less. This treatment was repeated until the fluid no longer reaccumulated. Patients were checked again 3 months later and then contacted at 6-monthly intervals. Doubtful cases were seen again in the clinic.

Results

Out of a total of 36 hydrocoeles, 1 has persisted after four injections but is still under treatment, which was interrupted by two myocardial infarctions. One hydrocoele has recurred a year after completing the initial course of treatment.

[illegible]YDROCOELE: [illegible]ETAILS OF TR[illegible]

[illegible]	No.*	No. of times injected (mean and range)	No. of times aspirated after initial treatment (mean and range)	[illegible] of OP visits (mean a[illegible] range[illegible]
[illegible]	1	1	1	4
[illegible]	15	1·6 (1–3)	1·5 (0–4)	4·1 (2–6)
2[illegible]00	13	1·8 (1–3)	2·1 (0–5)	4·3[illegible] (2–[illegible]
40[illegible]	6	2·4 (1–4)	3·2 (1–5)	[illegible]

* This excludes the one hydrocoele that has not bee[illegible]

Table II: EPIDIDYMAL CYSTS: DETAILS OF TREATMENT

Size of original aspirate (ml)	No.	No. of times injected (mean and range)	No. of times aspirated after initial treatment (mean and range)	Tota[illegible] no. of visits (mean a[illegible] range)
0–50	8	1·1 (1–2)	1 (0–2)	2·9 (2–4)
51–200	4	1·8 (1–3)	2 (1–3)	4·5 (4–5)
201–400	1	4	6	7

Table III: HYDROCOELES ASPIRATED MORE THAN TWICE BEFORE COMMENCING TREATMENT

Patient	No. of times aspirated	Frequency (mth)	Size (ml)	Cured (yr)
A	30	6	350	1¼
B	3	3	150	1¼
C	17	4	500	1½
D	5	3–6	200	2
E	8	3	270	1¾
F	20	6	550	1
G	50	3	260	1¼
H	20	3–6	750	1½

Table I shows details of the treatment required and the total number of outpatient visits in relation to the original volume of fluid aspirated. On average, the larger the hydrocoele the longer the course of treatment.

Treatment details of sclerotherapy for epididymal cysts are shown in *Table II*. The cysts tended to be smaller than the hydrocoeles and responded to treatment more readily. The distinction between hydrocoeles and epididymal cysts was necessarily made purely on clinical grounds and is open to some inaccuracy.

Table III illustrates the results of sclerotherapy in an important group of 8 patients who had been refused operation on grounds of ill health and had been attending the outpatient department every 3–6

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[illegible] roc[illegible] than 1[illegible] [illegible] nsation [illegible] fossa whi[illegible] was being injected. Two patients comp[illegible] ticular tenderness which lasted from 1 to 2 [illegible]

Six patients developed some degree of pa[illegible] thickening of the tunica vaginalis and epididymis; all of these patients had a hydrocoele greater than 250 ml which eventually became smaller so that the testis and epididymis were only slightly larger than on the other side. Two other patients have a residual swelling; one patient, who originally had a 475 ml hydrocoele, has a fibrous swelling above the testis about the size of a 50 ml epididymal cyst, and the other, who originally had a 550 ml hydrocoele, has a residual fibrocystic swelling approximately the size of a 100 ml hydrocoele. No patient has developed an infection.

Discussion

The results of this study show that sclerotherapy in the treatment of hydrocoeles and epididymal cysts is effective and free from all but minor side effects, and in 98 per cent of cases does not recur within an average follow-up of 18 months. These findings are comparable to those reported by Maloney (1975), who used a slightly different sclerosing agent.

At present the standard treatment of hydrocoeles and epididymal cysts is either repeated aspiration or operation (Pender, 1973; Whitaker, 1976; Rains and Ritchie, 1977). The former is not curative (*Table III*) and the latter has a high incidence of complications (Maloney, 1975). These can be minimized with careful surgery (Lord, 1964, 1970), but the development of a postoperative scrotal haematoma is notorious.

In conclusion, the present author would recommend surgery for fit patients under the age of 40, those suspected of having a testicular tumour and those with a hydrocoele greater than 500 ml. All patients refused operation on the grounds of ill health should be treated with sclerotherapy and for the remainder sclerotherapy is recommended but operation could be offered as an alternative.

Acknowledgements

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References

BRITISH MEDICAL JOURNAL (1973) Injecting hydrocoeles—an unproved treatment. (Any Questions.) 3, 344.

LANDES R. R. and LEONHARDT K. O. (1967) The history of hydrocoele. *Urologic Survey* **17**, 135–146.

LORD P. H. (1964) A bloodless operation for radical cure of idiopathic hydrocoele. *Br. J. Surg.* **51**, 914–916.

LORD P. H. (1970) A bloodless operation for spermatocoele or cyst of the epididymis. *Br. J. Surg.* **57**, 641–644.

MALONEY G. E. (1975) Comparison of results of treatment of hydrocoele and epididymal cysts by surgery and injection. *Br. Med. J.* **3**, 478–479.

PENDER B. W. T. (1973) Treatment of hydrocoele. *Practitioner* **210**, 586.

RAINS A. J. and RITCHIE H. D. (ed.) (1977) *Bailey & Love's Short Practice of Surgery*, 17th ed. London, Lewis, p. 1300.

WHITAKER R. H. (1976) Benign disorders of the testicle. In: BLANDY J. (ed.) *Urology*. Oxford, Blackwell Scientific, pp. 1194–1200.

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The ingrowing [illegible] [illegible]lifie[illegible] matrix excision [illegible]

S. S. GABRIEL, V. DALLOS A[illegible] J E [illegible]ENSON*

SUMMARY

A series of 528 patients with ingrowing toenails has been operated on under local anaesthetic by one surgeon using a simple technique in which a segment of germinal matrix is completely excised without cutting skin and with minimal interference with the nail wall. Normal footwear was worn by the fifth day in 79 p[illegible] of patients. The recurrence rate was [illegible] per cent.

INGROWING toenail is a common condition in the United Kingdom which causes the loss of many days from work by young adults. Lack of appreciation of the pathology of this condition has resulted in a large number of treatments which range from the wholly conservative approach (Lloyd Davies and Brill, 1963) to amputation of the distal part of the terminal phalanx (Thompson and Terwilliger, 1951; Rees, 1964; Townsend and Scott, 1966). In addition, there exist many operations which lie between these two extremes (Quènu, 1887; Watson-Cheyne and Burghard, 1912; Ney, 1923; Winograd, 1929; Heifetz, 1945; Zadik, 1950; Fowler, 1958; Palmer and Stevenson, 1976).

We believe that any operation for ingrowing toenail should satisfy the following criteria: the recurrence rate should be minimal; normal footwear should be worn with comfort within a week of the operation; a painless nail-bearing toe should be the end result; finally, the procedure should be simple.

An operation which satisfies these criteria has been developed by one of us (S. S. G.) and this paper gives details of the technique together with the results obtained in a series of 528 consecutive patients.

Patients and methods

A total of 528 consecutive patients with ingrowing toenails, attending the Accident and Emergency Department of Whipps Cross Hospital, London, over a 3-year period, was operated on by one surgeon (S. S. G.) using the technique described below. The age incidence is shown in *Table I*. Out of the series, 358 patients (68 per cent) were men and 170 (32 per cent) were women; 25 patients (4·7 per cent) were non-Europeans. In all cases it was the big toe that was affected and details of siting are shown in *Table II*. Twenty per cent (107) of the patients had previously undergone an operation for ingrowing toenail on one or more occasions. No antibiotic cover was used. Bilateral cases were treated on separate occasions.

The patients were followed up by a different doctor (V. D.) with the late results being assessed by a postal questionnaire 6 months to 3 years after the operation. If there was a recurrence the same operation was performed again.

The operation

The operation is performed using a local anaesthetic ring block of 3–5 ml of 1 per cent lignocaine without adrenalin.

A McDonald's dissector is introduced beneath the middle of the free edge of the nail and inserted as far as the lunular line. Keeping close contact with the undersurface of the nail, it is moved slowly from side to side, a manoeuvre which completely separates the nail from the nail bed. The nail is then gripped with artery forceps and removed with a gentle rolling motion.

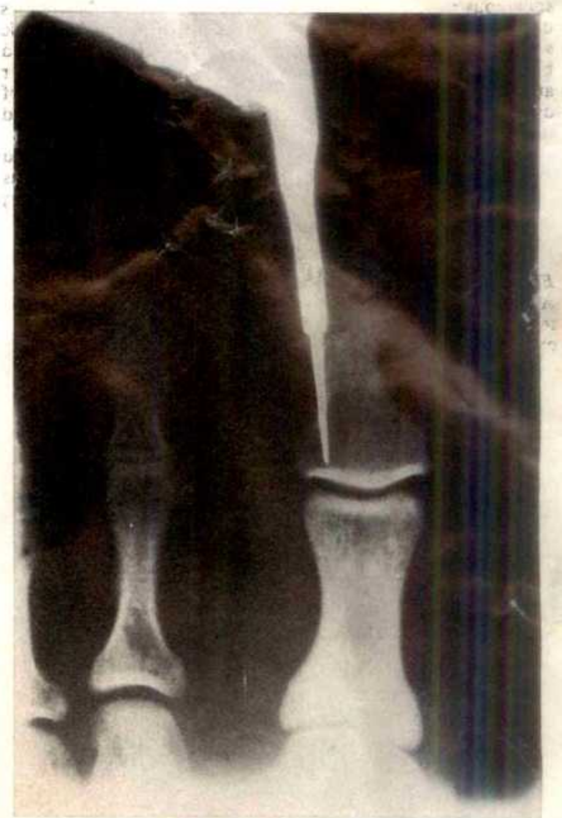

Fig. 1. Radiograph showing the scalpel incision into the nail bed and germinal matrix extending almost to the terminal interphalangeal joint.

A number 11 scalpel blade is used to make a longitudinal incision through the whole thickness of the nail bed and germinal matrix, marking out a narrow strip of tissue on the affected side about a quarter of the width of the germinal matrix and nail bed. The proximal limit of the incision in the matrix should be halfway between the lunular line and the terminal interphalangeal joint (*Fig.* 1). The nail fold is not incised and in order to facilitate the last part of the incision the nail fold is gently elevated on the back of the scalpel blade. The strip of tissue to be removed has now been clearly identified.

Small curved scissors are used to dissect the strip of tissue off the periosteum of the phalanx. The dissection starts distally with a small snip of the scissors at right angles to the initial incision. As the dissection proceeds, the strip of tissue is held by forceps and gently elevated until the point midway between the lunular line and the interphalangeal joint is reached. Here, the attachment of the germinal matrix ends so that separation at this critical level takes place naturally. No incisions in the nail fold are made.

The last step is to curette away any granulation tissue and then to excise carefully the epithelium on the inferior surface of

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* Whipps Cross Hospital, London E11.

[illegible] I:

[illegible] (yr[illegible]	
0–10	
11–20	
21–40	24[illegible]
40+	53

Table [illegible]TE OF LESION

S[illegible]	No. of patients	
Bilateral	127	
Unilateral	401	
Medial wall only	69	[illegible]
Lateral wall only	190	[illegible]3
Both walls	269	5[illegible]

Table III: TIME TAKEN TO RETURN TO NORMAL FOOTWEAR

Period	No. of patients	%
Up to one week	418	79
More than one week	110	21

the adjacent nail wall so as to ensure quick healing between the nail wall and the site of the excised nail bed. The number 11 scalpel blade is used for this manoeuvre.

Postoperative treatment

The wound is dressed with paraffin gauze and a pressure bandage applied. The patient is kept in the theatre area for half an hour with the foot elevated and is then sent home with instructions to keep the foot elevated for 24 h. Four days later the primary dressing is replaced by a smaller paraffin gauze dressing and the patient can then in most instances put on normal everyday shoes. At the next appointment, one week later, the patient is told that he can resume normal activities and is advised about the care of the new nail when it grows.

Results

Table III shows that 418 (79 per cent) of the patients returned to wearing their usual shoes within 1 week of the operation.

A total of 409 of the 528 patients completed the postal questionnaire showing late recurrence in 7 cases (1·7 per cent). These patients were recalled for further operation. There was no case of a second recurrence.

Discussion

The recurrence rate and morbidity associated with the surgical treatment of ingrowing toenail by traditional methods is high (Murray and Bedi, 1975) and we believe this series shows that both can be reduced to a more acceptable level. As far as we are aware there is no evidence to suggest that there is any difference in the recurrence rate between operations with complete excision of the germinal matrix and operations with [illegible]tal excision [illegible] mina[illegible]ix. It seems [illegible]erefore, tha[illegible] exc[illegible]s desirable so [illegible]tain the ad[illegible] a nai[illegible]ing toe. [illegible] widely kno[illegible]urre[illegible]ter operation [illegible]kes the forn[illegible]le of [illegible]djacent to the [illegible]all suggesti[illegible]senc[illegible] onychogenic [illegible]at this site. [illegible]re advocate excision of [illegible]ithelium on t[illegible]rface of the nail wall as [illegible]sted by Lapidu[illegible]o as to prevent this form [illegible]currence. Th[illegible]ecurrences recorded here [illegible]t all occurred [illegible]arly on in the series when it [illegible]sible that insu[illegible] care was given to this part [illegible] technique.

[illegible]noval of th[illegible] nail as a first step in the op[illegible]ion facilit[illegible]recise excision of the strip of na[illegible] be[illegible] and [illegible]nal matrix and makes skin incisions unnecessary. This avoids the need for suturing over a potentially infected area and gives a better cosmetic result. Removal of the whole nail also allows for better drainage of any infection that may be present.

A particular advantage of the operation we describe is that it is extremely simple and can therefore be safely undertaken by inexperienced junior staff.

References

FOWLER A. W. (1958) Excision of the germinal matrix: a unified treatment for embedded toe nail and onychogryphosis. *Br. J. Surg.* **45**, 382–387.

HEIFETZ C. J. (1945) Operative management of ingrowing toenail. *J. Missouri Med. Assoc.* **42**, 213–216.

LAPIDUS P. W. (1972) The ingrown toe nail. *Bull. Hosp. Joint Dis.* **33**, 181–192.

LLOYD DAVIES R. W. and BRILL G. C. (1963) The aetiology and outpatient management of ingrowing toenails. *Br. J. Surg.* **50**, 592–597.

MURRAY W. R. and BEDI B. S. (1975) The surgical management of ingrowing toenail. *Br. J. Surg.* **62**, 409–412.

NEY G. C. (1923) An operation for ingrowing toenail. *JAMA* **80**, 374–375.

PALMER B. V. and STEVENSON D. L. (1976) Modified operation for ingrowing toenails. *Br. Med. J.* **2**, 367.

QUÈNU M. (1887) *Bull. Soc. Chir. Paris* **13**, 252–255.

REES R. W. M. (1964) Radical surgery for embedded or deformed great toenails. *Proc. R. Soc. Med.* **57**, 355–356.

THOMPSON T. C. and TERWILLIGER C. (1951) The terminal syme operation for ingrowing toenail. *Surg. Clin. North Am.* **31**, 575–584.

TOWNSEND A. C. and SCOTT R. R. (1966) Ingrowing toenail and onychogryphosis. *J. Bone Joint Surg.* **48B**, 354–358.

WATSON-CHEYNE W. and BURGHARD F. F. (1912) *A Manual of Surgical Treatment*. London, Longmans, Vol. 2, pp. 27–30.

WINOGRAD A. M. (1929) A modification in the technique of operation for ingrown toenail. *JAMA* **92**, 229–230.

ZADIK F. R. (1950) Obilteration of the nail bed of the great toe without shortening the terminal phalanx. *J. Bone Joint Surg.* **32B**, 66–67.

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Loop col of colostomy i i

M. M. HENI KWOOD, V. HEMALATH

SUMMARY

The records of 0 consecut co closed at Adde dren is 1975 were stud pulmonary emb fistula from the cent.

A number of di ering 6 weeks after the colos op-tive antibiotic (ant nic obi aration appeared to be factors associa with favourable outcome. On the other hand, initial operation for carcinoma and closure less an 6 weeks after the colostomy's formation were factors related to a less favourable outcome.

THE incidence of complications following colostomy closure varies in different reported series. A high complication rate was reported by Knox et al. (1971) in a study of 179 colostomy closures performed in a major non-university centre, with a leakage rate of 23 per cent. That this operation is not necessarily attended by such a high morbidity rate is suggested by the results from St Mark's Hospital, London (Thomson and Hawley, 1972). In a series of 139 patients these authors reported an incidence of breakdown of only 2·9 per cent at the site of the colostomy closure. These operations were, however, performed by relatively experienced surgeons most of whom had a special interest in colorectal surgery. It is possible, therefore, that the results from the Exeter group (Knox et al., 1971) reflect more accurately the true hazards of the procedure when it is performed in a non-specialist centre. Barron and Fallis (1958) and Finch (1976), however, suggest that this is not necessarily so.

A retrospective analysis of the results of loop colostomy closure performed at Addenbrooke's Hospital was undertaken with two objectives. First, to compare the complication rate of this operation performed at our hospital with that of a specialist centre, and secondly, to assess any factors that may be associated with the development of complications.

Patients and methods

The records of 74 patients with loop colostomies closed during the period 1970–5 were analysed. The majority of these colostomies had been formed as part of a staged procedure in the treatment of distal colonic disease. All involved the transverse colon.

The average age of the patients was 63·5 years and the age distribution is shown in *Table I*. The male/female distribution was 1·7/1. In all cases a barium enema examination was performed before colostomy closure to demonstrate the integrity of the anastomosis and the absence of obstruction. Sigmoidoscopy was performed in some cases but not as a routine. The interval between formation and subsequent closure of the colostomy was less than 6 weeks in 41 patients (55·4 per cent) and more than 6 weeks in 33 patients (44·6 per cent).

The operations were performed by 16 surgeons: 39·2 per cent of the colostomies were closed by 3 consultants, 1 with a particular interest in colorectal surgery. The remainder were closed by registrars of widely differing experience.

ere was considerable variation in technique. All clos e intraperitoneal with drainage of both the anaston d the wound. In 83·8 per cent the ends of the colost ere resected while in the remainder the edges were trim nd the bowel approximated, leaving the posterior wall int reoperative mechanical bowel preparation was carried out ll patients: this included colonic washouts in the 48 h bef surgery. In 14 patients (18·9 per cent) antimicrobial bo preparation with oral phthalylsulphathiazole was also us Approximately 50 per cent of patients were treated w prophylactic antibiotics—tetracycline or penicillin a streptomycin.

The majority (77 per cent) of anastomoses were sutured one layer with interrupted Supramid; interrupted silk was u in 2 cases. The remainder (23 per cent) were sutured in layers using continuous catgut for the inner layer and interrupted silk sutures for the seromuscular layer.

Results

The postoperative course was uneventful in 62 of our 74 patients (83·8 per cent). One death occurred (1·4 per cent) in a 76-year-old man with malignant disease who developed a minor faecal fistula and wound infection. Both resolved spontaneously but the patient died from a pulmonary embolus on the eighteenth postoperative day.

Six patients (8·1 per cent) developed a faecal fistula. Two of these fistulas, however, were from the distal anastomosis rather than from the site of the colostomy closure. Both these patients showed evidence of leakage within 24 h of surgery. One had an extensive collection of pus drained from beneath the original laparotomy wound. The other became septicaemic but responded to a course of parenteral antibiotics and no further surgery was necessary. The intervals between formation and closure of the colostomy in these patients were 3 weeks and 3 months respectively. In both cases a barium enema examination performed before closure showed a small leak which had apparently sealed and an otherwise sound anastomosis.

Only 4 (5·4 per cent) of our patients developed a leak from the site of the colostomy closure. In none was this associated with septicaemia and all the leaks closed spontaneously with conservative management.

In *Table II* the various factors that might have been associated with the development of complications are listed. The group of 4 patients who developed fistulas from the site of the colostomy closure is compared with the majority who did not. Since the number of patients with this complication was small, no attempt was made to draw a statistical comparison.

It is of interest to note that no faecal fistulas developed in those patients whose operations had been performed by a consultant, although nearly 40 per cent of all the colostomies had been closed by a surgeon of this seniority. Similarly, fistulas did not occur in any patient who had received preoperative antimicrobial bowel preparation nor in those whose colostomies had been closed more than 6 weeks after formation. All 4 patients who developed a faecal fistula had had resections for carcinoma and

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61–7
11 71–80
14 80+

Table II: FACTORS CONSIDERED TO BE RELATED TO THE INCIDENCE OF COMPLICATIONS: COMPARISON OF THE PATIENTS WHO DEVELOPED A FISTULA FROM THE SITE OF THE COLOSTOMY CLOSURE WITH THOSE WHO DID NOT

	Faecal fistula	No faecal fistula
of patients	4 (5·4%)	70 (94·6%)
ale)	3 (75%)	44 (62·9%)
ge (yr)	65	64·3
lactic antibiotics	1 (25%)	36 (51·4%)
otic bowel preparation	0 (0%)	14 (20%)
eration by consultant	0 (0%)	29 (41·4%)
erval (wk)		
<6	4 (100%)	37 (52·9%)
>6	0 (0%)	33 (47·1%)
Carcinoma	4 (100%)	52 (74·3%)
Formal excision	4 (100%)	58 (82·9%)
One-layer anastomosis	3 (75%)	54 (77·1%)

Table III: FACTORS CONSIDERED TO BE RELATED TO THE INCIDENCE OF COMPLICATIONS: COMPARISON OF PATIENTS WHO DEVELOPED A WOUND INFECTION IN THE ABSENCE OF A FISTULA WITH THOSE WHO DEVELOPED NO COMPLICATIONS

	Wound infection	No complications
No of patients	6 (8·1%)	62 (83·8%)
Sex (male)	3 (50%)	40 (64·5%)
Mean age (yr)	60·8	64·7
Prophylactic antibiotics	3 (50%)	33 (53·2%)
Antibiotic bowel preparation	0 (0%)	14 (22·6%)
Operation by consultant	4 (66·7%)	25 (40·3%)
Interval (wk)		
<6	4 (66·7%)	32 (51·6%)
>6	2 (33·3%)	30 (48·4%)
Carcinoma	6 (100%)	44 (71·0%)
Formal excision	6 (100%)	50 (80·6%)
One-layer anastomosis	5 (83·3%)	47 (75·8%)

their colostomies had been closed by the technique involving excision of the bowel ends. It would appear from these results that age, sex, prophylactic antibiotics and one-layer anastomosis are factors that do not influence the incidence of fistulas from the site of closure.

Wound infections occurred in all patients who developed a leak from the site of the colostomy closure. A further 6 patients developed wound infections without the coexistence of a faecal fistula. The various associated factors are listed in *Table III*, comparing these 6 patients with the 62 patients who were free of complications.

Age, sex, prophylactic antibiotics, one-layer anastomosis and the interval before closure do not appear to be factors relevant to the development of wound infection.

in … o the fistula group, 4 of the 6 patients … a wound infection had been operated … t. The groups were comparable, how… f the wound infections occurred in … rcinoma whose colostomies had … ing formal excision f the bowel … nt treated preopera ely with an … aration developed a wound in-

al leakage from the site of … ·4 per cent in our series. This … the figure of 2·9 per cent … k's Hospital (Thomson and Hawley, … 's perhaps explained by the fact that the majority of our cases were operated upon by relatively inexperienced surgeons and that, of the 3 consultant surgeons, only 1 had a special interest in colorectal surgery. The fact that all 4 patients who developed a leak had been operated on by registrars supports this contention. Also, as the St Mark's group admit, there must be some degree of case selection in their series. Their results may not, therefore, be truly representative.

Our results compare favourably with the 9 per cent incidence of faecal fistula reported from Oxford (Finch, 1976) and the 23 per cent incidence from Exeter (Knox et al., 1971). However, a larger number of patients were studied in each of these series.

In addition to the patients who developed a wound infection in association with a faecal fistula, a further 6 patients (8·1 per cent) developed a postoperative wound infection alone. Excluding the 2 patients who leaked from the distal anastomosis, there was an overall incidence of wound infection of 13·5 per cent. This compares with 17·2 per cent from St Mark's Hospital and 33 per cent from the Oxford and 30 per cent from the Exeter groups. Different criteria for assessing the presence of wound infection may account for these differences.

Because of the small number of patients in our series, it is difficult to determine the factors that may be associated with either a greater or a lesser risk of complications following this procedure. However, none of our patients who had been treated preoperatively with an antimicrobial bowel preparation developed complications. Finch (1976) found that the incidence of faecal fistula in patients not having had antimicrobial bowel preparation was twice that seen in the other group. Dixon and Benson (1944) similarly found that the incidence of faecal leakage fell from 30 per cent to 2 per cent in those treated preoperatively with succinylsulphathiazole and sulphathiazole. In this series the incidence of wound infection fell from 84 per cent to 13 per cent following the use of antibiotics, whereas Finch (1976) found the wound infection rate to be similar in the two groups. In contrast, in our series the use of oral or systemic antibiotics did not appear to affect the incidence of wound infection, although only 1 of the 4 patients who developed a leak had been treated preoperatively with antibiotics.

That closure of a colostomy performed within 6 weeks of its creation should be associated with an increased risk of developing a fistula is unexplained. Thomson and Hawley (1972) found a high risk of complications if the colostomy was closed within 28

days and they attributed this to [illegible]
culties created by the early oedema [illegible]
of the colostomy which may occur. [illegible]

The presence of underlying mali [illegible]
a constant factor in all our patien [illegible]
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ticular disease, although the fig [illegible]
by statistical methods.

None of our patients was recorded as having developed an incisional hernia at the colostomy site, although this was a frequent finding in other series. Although this low incidence may have been due to failure to look for and record this complication, it may also reflect the success of nylon as a suture material for closing wounds, since virtually all the wounds in our series were closed with one layer of continuous double nylon (metric 3). The advantages

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References

BARRON J. and FALLIS L. S. (1958) Colostomy closure by the intraperitoneal method. *Dis. Colon Rectum* **1**, 466–470.

IXON C. F. and BENSON R. E. (1944) Closure of colonic stoma improved results with combined succinylsulfathiazole an sulfathiazole therapy. *Ann. Surg.* **120**, 562–571.

EVERETT W. G. (1970) Suture materials in general surgery. *Pr* [illegible] *Surg.* **8**, 15–37.

FINCH D. R. A. (1976) The results of colostomy closure [illegible] *Surg.* **63**, 397–399.

JENKINS T. P. N. (1976) The burst abdominal wound: a [illegible] anical approach. *Br. J. Surg.* **58**, 873–876.

KNOX A. J. S., BIRKETT F. D. H. and COLLINS C. D. (1971) Cl [illegible] of colostomy. *Br. J. Surg.* **58**, 669–672.

THOMSON J. P. S. and HAWLEY P. R. (1972) Results of closure [illegible] loop transverse colostomies. *Br. Med. J.* **3**, 459–462.

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s technique:

[illegible]s technique has been used to close 238 abdominal wounds. No dehiscence occurred in this series. It is suggested that this method, which gives strict guidelines on wound closure, is ideal for teaching good technique for wound closure.

In 1976 Jenkins stated that the burst abdominal wound has a mechanical cause, being the result of suture breaking, knot slipping, the intact suture cutting out of the tissues or protrusion of gut or omentum between the sutures (Jenkins, 1976). These factors were considered to be due to the wound lengthening by as much as 30 per cent if distension occurred. It was suggested that wound disruption can be avoided by using a suture length four times as long as the wound, and by placing non-absorbable sutures at 1-cm intervals and more than 1 cm from the wound edge. To test this hypothesis a prospective study was made of 238 consecutive wound closures in 219 patients. These wound closures were performed by the author, or by another member of the junior staff under supervision, between May 1976 and April 1978. The nature of the operations and the incisions used are shown in *Tables I* and *II*.

Table I: ANALYSIS OF 238 ABDOMINAL WOUNDS IN 219 PATIENTS ACCORDING TO THE NATURE OF THE OPERATIVE PROCEDURE*

Nature of operation	No.
Ileum, colon and rectum	70
Biliary and pancreas	60
Upper GI tract	29
Kidney and ureter	12
Arterial	10
Laparotomy only	6
Trauma	5
Bladder	4
Appendix	3
Other	39

* If more than one system was operated upon, the major operation is listed.

Table II: ANALYSIS OF 238 ABDOMINAL WOUNDS IN 219 PATIENTS ACCORDING TO THE TYPE OF INCISION

Type of incision	No.
Transverse	50
Upper paramedian	49
Upper midline	30
Lower paramedian	28
Paramedian	26
Midline	15
Lower midline	14
'Kocher' (left or right)	13
Oblique	8
Pfannenstiel	5

Technique

The incisions were closed with continuous [illegible] nylon (metric 3·5 Ethilon) on a 40-mm round-bodied half-circle needle (Ethicon W 740) using suture length to wound length ratios of greater than 4 : 1 and large tissue bites of greater than 1 cm. The wounds were closed in layers whenever possible. Mass closure was used if the layers were obliterated or if adequate layered bites could not be obtained. Midline incisions were closed in one layer, paramedian incisions were closed in two layers and transverse or oblique incisions were closed in the layers present at the particular site. The peritoneum was closed separately only if this facilitated the muscle closure by reducing the viscera, otherwise it was included with the deepest muscle layer. The nylon suture was tied with a triple-layer surgeon's knot and the ends cut flush with the knot to leave no tails.

Results

All wounds were reviewed at 6 weeks. No wound dehisced during the period of the study, and at 6 weeks there was no evidence of an incisional hernia. None of the 38 patients who died (17·4 per cent) showed a primary wound failure.

Discussion

To gain acceptance any new surgical technique must provide good results in the hands of others. Such techniques should be uncomplicated, easily learned and, if possible, universally applicable without special equipment. The ability to close abdominal wounds is a prerequisite for all surgeons in training before other procedures can be undertaken. Surprisingly, few guidelines are given to the trainee, and these cannot be accurately defined. The technique under consideration has the great merit of providing accurate measurements, which can guide the novice.

This study confirms the results reported by Jenkins (1977) and shows that the technique can be learnt by the trainee, with good initial results. It would seem that this study supports the hypothesis that bursting of the abdominal wound has a mechanical cause; furthermore, dehiscence can be prevented by overcoming this mechanical cause of wound failure.

Acknowledgements

I wish to acknowledge the invaluable assistance given to me by Mr R. G. Notley in drafting this paper.

References

JENKINS T. P. N. (1976) The burst abdominal wound: a mechanical approach. *Br. J. Surg.* **63**, 873–876.

JENKINS T. P. N. (1977) Burst abdomen—a preventable condition? *Br. Med. J.* **1**, 771–772.

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nd to be surrounded by vascular granulation t
a tongue of bone cement which protruded
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mpartment of the ischiorectal fossa (*Fig.* 3). A s
assed into the hip wound presented in the peri
mponents of the hip joint were removed, and
during the operation produced haemolyt
(Lancefield Group C). Postoperatively she
faeculent discharge through her hip wound an[illegible]
treated by a transverse colostomy. Following this, she
rapid and uneventful recovery and when last seen s[illegible] as
[illegible]king well with two sticks and her faecal fistula and [illegible]
sinus had healed. The colostomy was closed without in[illegible]
[illegible] year after the removal of her hip prosthesis.

Discussion

Infection of prosthetic joints is a serious complication of joint replacement surgery and may necessitate removal of the prosthesis and conversion to a Girdlestone pseudarthrosis. Infection may be early or late. Early infection occurring in the immediate postoperative period is usually clinically obvious, but infection occurring several months after surgery may be difficult to identify. Late infection is thought to be due to wound contamination during surgery or to haematogenous spread from a septic focus (Coventry, 1975). Late infection of total hip replacements following haematogenous spread from a septic focus is well documented (Mallory, 1973; Creuss et al., 1975; Downes, 1977), but precise proof of late infection occurring due to contamination at the time of surgery has not yet been produced. In our own patient, it would seem unlikely that the origin of sepsis was contamination of the wound at surgery because both the replacements were carried out in a sterile environment and extensive bacteriological monitoring revealed no organisms. The site of presentation of the infection and the unusual nature of the organism makes it likely that it was caused by haematogenous spread from perhaps a minor focus of sepsis which passed unnoticed by the patient. Indeed, Downes (1977) has made a plea for the treatment of any potential sources of infection before replacement surgery and also after any procedure liable to produce a bacteraemia.

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[illegible]ical suspicion that this was no ordinary ischiorectal
[illegible]scess should have arisen earlier as haemolytic *S. pyogenes* is not an organism commonly grown from such abscesses. Indeed Page and Freeman (1977) have found that only 4·7 per cent of perianal suppuration in their series was due to *S. pyogenes*.

It is well documented that colonic or rectal pathology can present with sepsis in the upper thigh or buttock (Main et al., 1977), but we believe that this is the first case of hip sepsis to present perineally. Considering the intimate relationship of the acetabulum to the ischiorectal fossa perhaps it is surprising that it is not more common.

References

BURTON D. S. and SCHURMANN D. J. (1977) Salvage of infected total joint replacements. *Arch. Surg.* **112**, 574–578.

COVENTRY M. B. (1975) Treatment of infections occurring in total hip surgery. *Orthop. Clin. North Am.* **6**, 991–1003.

CREUSS R. L., BICKEL W. S. and VON KESSLER K. L. (1975) Infection in total hips secondary to a primary source elsewhere. *Clin. Orthop.* **106**, 99–101.

DOWNS E. M. (1977) Late infection after total hip replacement. *J. Bone Joint Surg.* **57A**, 42–44.

MAIN W. S. J., MCADAM W. A. F., LEE P. W. R. et al. (1977) Carcinoma of large bowel presenting as a subcutaneous abscess of the thigh, a report of 4 cases. *Br. J. Surg.* **64**, 205–209.

MALLORY J. H. (1973) Sepsis in total hip replacement following pneumococcal pneumonia. *J. Bone Joint Surg.* **55A**, 1753–1754.

PAGE R. E. and FREEMAN R. (1977) Superficial sepsis: the antibiotic of choice for blind treatment. *Br. J. Surg.* **64**, 281–284.

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Late infection of a total hip rosthes as an ischiorectal abscess

R. D. BRIGGS, J. MCLAUCHLAN AND A. DAVIDSON*

SUMMARY

Late infection of a total hip arthroplasty recently presented as an ischiorectal abscess. A likely pathogenesis is suggested and the literature on late infection in prosthetic joints is reviewed.

Case report

A 68-year-old lady presented in 1972 with a 4-year history of bilateral hip pain of gradually increasing severity. Clinically, this was attributed to osteoarthritis of both hips and this was confirmed radiologically.

In early 1973, bilateral total hip arthroplasties were carried out, a surgical isolator being used during both operations. Bacteriological monitoring of the wound and environment throughout operation was negative and the postoperative period was uneventful. The patient was discharged from hospital after 5 weeks. She was reviewed in the outpatient department on several occasions over the following 6 months and was discharged in late 1973, pain-free and walking without aid.

In June 1976 she noted vague pain in her right hip, but thought nothing of it. In the intervening period, she had been symptom-free and in excellent general health. She was admitted to hospital late in June 1976 with an ischiorectal abscess which was incised and drained. Culture of the pus obtained produced a haemolytic *Streptococcus pyogenes* (Lancefield Group C). Following this procedure, the pain in her hip appeared to improve, but she continued to discharge pus from the abscess cavity over the following 4 months. This was attributed to a fistula-in-ano, but an examination under anaesthetic failed to delineate the postulated fistulous track. The sinus was explored and curetted on two occasions, but persistently failed to heal.

In December 1976 she was complaining bitterly of pain in her right hip and a radiograph at this time revealed central subluxation of the acetabular component of the right total hip prosthesis (*Fig.* 1).

She was admitted to hospital and the pain improved with conservative measures including bed rest, traction to the right leg and a lumbosacral belt. She was discharged home after 2 weeks but her perineal sinus continued to discharge.

Over the next few months her hip became increasingly painful and she was readmitted in March 1977 for further investigation. An anteroposterior radiograph of her pelvis at time showed central subluxation of the right hip prosthesis was transferred to Aberdeen Royal Infirmary in June 197 with intractable pain in her right hip. On admission she wa cachectic with fixed flexion of her right hip, any movement of which produced excruciating pain. Her haemoglobin was 9·9 g with a blood film suggestive of an iron deficiency anaemia. As she still had a perineal discharge, it was felt that she migh

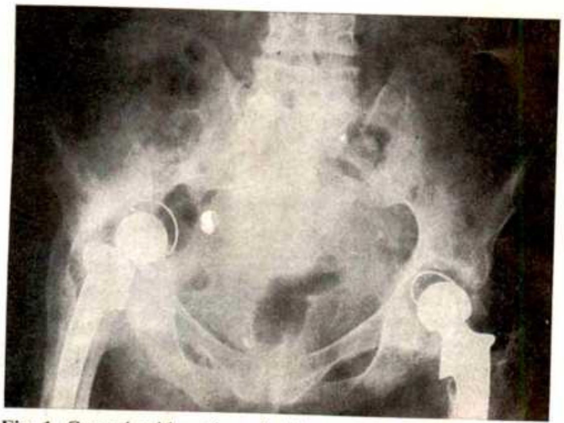

Fig. 1. Central subluxation of right total hip prosthesis.

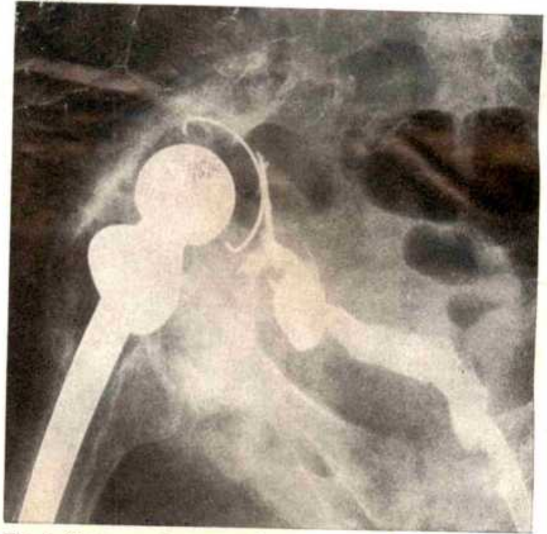

Fig. 2. Sinogram demonstrating sinus track between perineum and right hip joint.

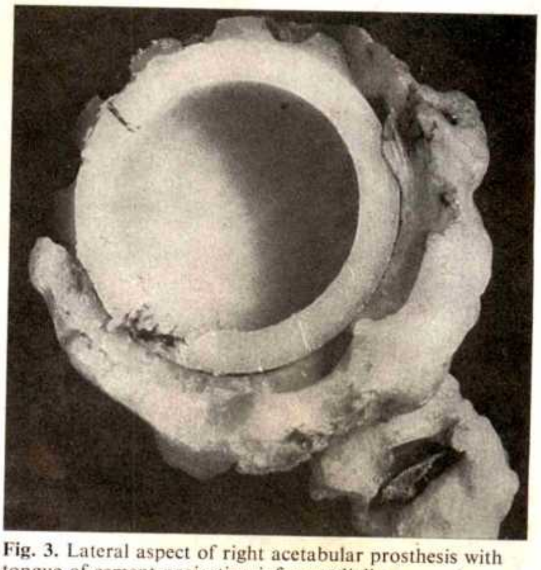

Fig. 3. Lateral aspect of right acetabular prosthesis with tongue of cement projecting inferomedially.

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* The Royal Infirmary, Aberdeen.

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On survival rates in surgical [illegible]

Sir,

K. A. Myers and his co-aut[illegible] Surgical treatment of the sev[illegible] rates. *Br. J. Surg.* **65**, 460–464) [illegible] labours and for adopting the li[illegible] assessing the results. Yet, a clo[illegible] educes some anxiety as to the interpret[illegible] as to any justification for optimism. [illegible]

Inspection of any life survival [illegible]le [illegible] passing of time, the number o[illegible]vive[illegible] mortality theorists have endeavo[illegible] pr[illegible] an 'attrition force' which would exp[illegible]d p[illegible] and the slope of the curve. Recent [illegible] (Strehler and Mildvan, 1960) assumes that there exists a *force of mortality* which tends to displace the individual from the condition of being alive to one of being dead, and that the individual reacts by calling upon his reserves of *vitality* in order to resist this displacement. This vitality (the Gompertz component of Strehler and Mildvan) is an age-dependent function and it diminishes with the passing of time; but the force of mortality is environmental and its strength varies (i.e. the vitality of an individual suffering from a cold would come under attack by a force of mortality not quite as powerful as if he were suffering from meningitis).

By this thinking, one might anticipate that by exposing one of two equivalent populations to an increased force of mortality, then the survivorship curve for the challenged group should show a steady downward displacement (i.e. a reduction in the number of survivors), which should last until the effects of the agency are exhausted, at which time the two curves should assume parallel courses. Experimental evidence from mice exposed to halothane (Boba and Drews, 1966) and the study of life expectancy after diagnosis of cancer of the breast (Mueller et al., 1978) confirm these assumptions.

We may now comment on the authors' figures:

Fig. 7: The survivorship curve for patients with myocardial ischaemia should, and it does, exhibit a divergent downward path from that of patients free of it (the former group being, in fact, exposed to a greater force of mortality).

Fig. 6: Here the same considerations prevail, except that the curves begin to diverge 1 year later.

Fig. 8: After the force of mortality effects specific to each presenting symptom are exhausted, the survival curves follow parallel paths, just as expected.

Fig. 5: The steadily divergent curves from zero time onward would support the assumption that symptomatic leg ischaemia is an agency with an intrinsic and continuous force of mortality. However, this is an artefact secondary to the expansion of the left side of the time scale (once this is corrected one obtains a duplicate of *Fig.* 3).

Fig. 3: The initial sharp fall in the survivorship curve for patients in the study is an effect of the specific force of mortality of symptomatic leg ischaemia *and of the treatment.* This effect lasts about 2 years, and after that time the curves continue to diverge, but *at a much slower rate.*

The following alternate conclusions are now proposed:

1. Symptomatic leg ischaemia indicates a sudden discrete increase in the force of mortality applied to the patient. The curve indicates that its effects *and the effects of treatment* last about 2 years; thereafter these patients continue to be at a somewhat increased risk (probably entirely accounted for by such concom[illegible] diseases as diabetes and myocardial ischaemia, as shown [illegible] 7).

2. There were [illegible]s performed in 411 patients at or about the time [illegible] symptomatic ischaemia. If any of this had been of s[illegible]alue, then the survival curve for patients operated upo[illegible] follow a course parallel to that of the general population, a[illegible]r a short-lasting initial downward displacement because of anaesthetic and operative m[illegible]ity; yet *Fig.* 3 shows that this is clearly not the case.

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[illegible]ould give serious consideration to the [illegible] [illegible]urvivorship alone, better results might be obtai[illegible] [illegible]were directed towards (*a*) early and aggress[illegible] (i.e. reduce the number of anaesthetics and ope[illegible] [illegible]he number of hospital days); (*b*) early ambulatio[illegible] [illegible]ntroduction of necessary changes in life-style (sto[illegible] [illegible]r control of diabetes etc.).

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BOBA A. and DREWS J. (1966) Effects of halothane on [illegible] expectancy of mice. *Can. Anesth. Soc. J.* **13**, 282–289.

MUELLER C. B., AMES F. and ANDERSON G. D. (1978) Breast cancer in 3558 women: age as significant determinant in the rate of dying and causes of death. *Surgery* **83**, 123–132.

STREHLER B. L. and MILDVAN A. S. (1960) General theory of mortality and aging (a stochastic model relates observations on aging, physiologic decline, mortality and radiation). *Science* **132**, 14–21.

Perforated appendix—a plea for lavage

Sir,

Greenall and his colleagues (*Br. J. Surg.* **65**, 880–882) have investigated the value or otherwise of an intraperitoneal drain in patients with perforated appendix. Over an 8-year period major wound sepsis occurred in 50 per cent of patients in whom a drain was inserted and in 44 per cent in whom drainage was avoided.

The signal benefits of antibiotic peritoneal lavage in gross peritoneal contamination have been established experimentally (Stewart and Matheson, 1978b) and antibiotic lavage of the peritoneal cavity and of the wound in patients with bacterial contamination has been our routine for some 13 years. In 58 children with perforated appendix in whom the peritoneal cavity was washed out with tetracycline in saline, the incidence of purulent discharge from the incision was 8·6 per cent compared with 29·2 per cent in 72 similar children treated during the same 10-year period (1965–74) without lavage (Stewart and Matheson, 1978a).

During 1977 and 1978 we have kept a wound record in all adults under our care in whom operation involved opening the peritoneal cavity. During this 2-year period, excluding patients in whom the appendix was obviously normal, 64 patients were operated on for appendicitis. Lower midline incisions were used in 4 and grid-iron incisions in the remainder. Neither peritoneal nor wound drains were used except in one patient in whom a wound drain was inserted contrary to general policy. All wounds were closed primarily. Wound infection as evidenced by purulent discharge was not recorded during the hospital stay of any of these patients, but one patient, sent home 7 days after a lower midline incision for appendicitis with an established abscess, returned some days later with wound infection. The longest stay in hospital was 10 days after operation and the mean duration of stay was 5 days. It is possible that, unknown to us, wound infection may have occurred in some of these patients after discharge from hospital and, furthermore, the appendix was perforated only in a small minority, so that we do not regard these observations as comparable to those of Greenall et al. (1978). None the less, they strengthen our conviction that neither wound sepsis nor residual intraperitoneal infection need be much of a problem after appendicectomy and that drains are neither necessary nor desirable. In all these patients the peritoneal cavity was washed out locally, usually with about 400 ml of saline containing 1 mg/ml tetracycline, the remainder of the 500-ml

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N. A. MATHESON

LOCK (1978) Should
dis? Br. J. Surg. 65, 880–

(19 8a) Peritoneal lavage in
Surg. 65, 54–56.
(1978b) Peritoneal lavage in
r. J. Surg. 65, 57–59.

ok reviews

Radiology of the Ear, Nose and Throat

el and Glyn A. S. Lloyd. Second edition. 24
with 330 illustrations. 1978. London: Lewis.

d edition of Samuel's well-known book on of the ear, nose and throat is a very welc the library of the ENT surgeon. The coverage of the ial is very clear and didactic and certainly all the owledge required for those reading for higher examin ons in ear, nose and throat surgery is well covered. The t ould have been improved if the authors had also taken clinical advice about matters beyond their field: at several points statements are made which are either untrue or unfamiliar; for instance, the terms 'intrinsic' and 'extrinsic' carcinoma of the larynx have not been in use by clinicians for twenty years or so.

The book is beautifully produced, easy to read and clearly written, with the exception of the authors' irritating habit of the use of the word visualize; I hope that radiologists see things and do not imagine them!

This book is a classic in its field and is essential reading for the ENT surgeon in training, for the established consultant and for those required to give postgraduate instruction. It should also be an essential part of the library of any district general hospital with a full ENT department.

P. M. STELL

Boies's Fundamentals of Otolaryngology: A Textbook of Ear, Nose and Throat Disorders

Edited George L. Adams, Lawrence R. Boies and Michael M. Paparella. Fifth edition. 230 × 155 mm. Pp. 746 + xix. 1978. Philadelphia: Saunders. £12·50.

THIS textbook, which was first produced in 1949, is now in its fifth edition, nearly 30 years later. It claims to be a standard textbook for medical students and house officers. It also includes, in addition to the standard ENT text, a small section on facial plastic surgery.

One would have to be a devoted student to wish to read so large a text and it is certainly well beyond the needs of any British student taking his final MB examination and compares unfavourably both in detail and cost with simpler textbooks available in paperback. For a house surgeon it would prove a useful source of reference, but again there are simpler texts at a much lower cost. For those wishing to take the final fellowship in ENT it would not be sufficient, but for those taking the DLO it might well prove worth while. As a general comment, the book contains much of solid worth, which is easily assimilated, but several conditions, which many would regard as quite rare, seem to receive an attention which is out of proportion.

For me the biggest disappointment was that in many parts of the book, no approximate statistical information is given as to the prevalence of many of the conditions, thereby guiding the reader as to the emphasis he should place in his reading.

The book is well and simply illustrated, but those reading the section on audiology must remember to consult the key before so doing, as the international range of symbols is not used.

J. B. BOOTH

Diseas nd Other iseases of the enta an d en

d P Ch. Her er and J. revot. 224 ×
m. illustrat ns. 1978. Munich: Urban
nwa L 8.

is book recur s ly the proce ings of an international symposium on ulcer e co tis and Crohn's disease sponsored by the Austrian A ion of Paediatric Surgeons in January 1976. Some other p which were not given at the symposium have been incl

There are five s of various forms of treatment of ulcerative colitis, including the use of salazopyrine and steroids and the follow-up results of operations for ulcerative colitis in children, the long term results of medical treatment and a discussion of immunosuppressive treatment in ulcerative colitis in childhood. Another chapter discusses a clinical survey of the symptoms, associated diseases and local and metabolic complications of Hirschsprung's disease and the treatment with various drugs and immunosuppressive agents. Another study considers 19 children and 160 adults with Crohn's disease with particular reference to the features of the disease in children and their management, and it is emphasized that the risk of relapse is greater when the disease involves the ileum and the proximal colon than when it is more distally situated in the colon. A chapter on neonatal necrotizing enterocolitis emphasizes the early onset of this disease; many patients begin to suffer from it within 24 h of birth and the mortality rate remains high, even though the birthweight in this particular series was greater than in most other reported series. Another paper discusses the implications for operation in necrotizing enterocolitis and the type of procedure which is carried out. In addition, there is a chapter on 82 patients with congenital duodenal obstruction, another on portal hypertension, a most interesting paper on the history of malformations of the anus and rectum and another on cystic lymphangiomas infecting various organs within the abdomen.

This series of papers is of interest mainly to paediatric surgeons, to whom it can be recommended.

A. W. WILKINSON

1001 Multiple Choice Questions and Answers in Surgery

A. J. Harding Rains. 197 × 130 mm. Pp. 221 + ix. 1978. London: Lewis. £4·00.

THIS collection of MCQs in sur y was obviously designed as a revisional exercise on the contents of *Short Practice of Surgery* and should be of value to those students using this textbook. The questions, some of which are validated by computer analysis, are either of the single-response variety or the determinate-response kind. The vast majority of questions included in the book relate to f al knowledge on the subject and few, if any, of th tions have problem-orientated stems that test the a to manage a specific clinical situation.

Apart from this omission, the questions are well thought out and clearly expressed and cover the essentials of the subject.

A. CUSCHIERI

Basic Surgical Technique

R. M. Kirk. Second editi
1978. Edinburgh: Church

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THE first edition of this
1973 and was very well
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principles of 'how to do it' K.
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surgery as how to handle a le as a of
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how to handle yourself—the
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'Most operators work best in a
calm . . . .'

The book is well pro ed and ad
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comprehensive.

This book can be thoroughly reco nded to all whe
undertaking a surgical apprenticeship ed indeed it ca
recommended to their teachers too.

BRENDAN DEV

The Acute Abdomen for the Man on th et

J. C. Angell. Third edition. 215×1 n. Pp. 116. 1978. Tunbridge Wells: Pitman Medical. £1

THIS is just the book for the inexperienced house surgeon or junior registrar. It is short and written in an easy, colloquial manner; it could easily be read between being appointed and taking the post. It is full of sound advive about the acute abdomen. The great asset of the book is the fact that it is an account of the author's own experience and what he has observed. He does not hesitate to give an account of his own mistakes and what he has learnt from them. All would-be surgeons should read this book. It will be of great practical value.

A. B. BIRT

Management of Primary Bone and Soft Tissue Tumors

Proceedings of the Annual Clinical Conference on Cancer at the University of Texas, M. D. Anderson Hospital and Tumor Institute. 230×150 mm. Pp. 474. Illustrated. 1977. London: Year Book Medical Publishers. £31·00.

THE Year Book Medical Publishers produce eminently readable, organized tomes with beautifully reproduced histology and radiology. The proceedings of the Annual Clinical Conference from Houston in 1976 is no exception. The management of primary bone and soft tissue tumours is discussed by staff members of the M. D. Anderson Hospital and invited speakers. The first two contributions are by the Heath Memorial Award recipients; Dr Franz Enzinger giving his usual didactic and lucid exposition on benign lipomatous tumours simulating sarcomas, which has the authority we associate with this author, and Dr Wataru Sutow relating the changes in the treatment of rhabdomyosarcoma and osteosarcoma in children to chemotherapy policy. There is quiet insistence by several authors that the prognosis in bone and soft tissue sarcomas has definitely improved owing to the addition of aggressive chemotherapy schedules and that this will be reflected by long term sur al as well as in increased disease-free intervals. Other outstan g chapters include a review of the histological classification of bone tumours by Harlan J. Spjut and appraisals of the place of conservative or radical surgery in bone and soft tissue sarcomas.

Although it is easy to criticize the publication of proceedings on the grounds of patchily covering the subject and the fact that such up-to-date are already past history by the time they appear in p is book is a worth-while statement. The chapters are by acc ed experts in a fast-moving field and give an overall review, in many instances, of the state of play at present. I think it is a useful, albeit expensive, addition to any oncological, orthopaedic or pathological department library.

MARGARET SPITTLE

h
d is
introduction to the subject prim
and those involved in sports
h example. However, medical students w
dip into as an introduction on the subject.
substance of the book sets out trauma
s helped by well-thought-out line drawings a
more concerned with soft tissue injuries
s, although reference is made to the co
ne injuries. This part of the book is follo
on on emergency first aid for injuries
The main types of treatment which
to soft tissue injuries are then briefly di
aspects include a short and practical guide to the
of sports injury service and the book ends with a use
sure that this publication, produced thr
auspices of Bayer UK Ltd, will find its way into mo
clubs and several copies on the bookshelf of sp
medical officers would be of value for circulation am
concerned in this field.

MICHAEL A. EDGAR

Atlas of Endoscopic Retrograde Cholangiopancreatography

Edited Edward T. Stewart, Jack A. Vennes and Joseph E. Greenen. 290×215 mm. Pp. 366+xvi, with 367 illustrations. 1977. St Louis: Mosby. £35·45.

THERE is ample justification for an atlas of this kind now that endoscopic retrograde cholangiopancreatography (ERCP) is so widely used in the investigation of pancreatic and biliary tract disorders. It is generally agreed by those with experience of ERCP that radiograph interpretation is far the most difficult aspect of the procedure. Biliary tree radiology is already familiar but pancreatograms are not and, contrary to the advice of the authors of this atlas, many endoscopists do not have the assistance of an interested radiologist.

This volume is both a manual of ERCP as well as an atlas of radiographs, and as such it includes lucid chapters on endoscopic and radiological technique. In the section on endoscopic technique there is surprisingly little emphasis on the use of the short route to the papilla, which is only mentioned as an alternative manoeuvre if initial attempts at cannulation are unsuccessful, although it gives better control and reduced irradiation of the fibre bundle. There is no reference to the use of hyoscine butylbromide (Buscopan) as a duodenal relaxant because it does not have FDA approval in the United States although it is widely used in this country. A section on the endoscopic appearances of the duodenal loop and papilla would not have been out of place, since the endoscopic examination forms an integral part of the whole procedure.

The atlas itself is well planned and executed with a full and comprehensive index. Descriptions of the embryological development and normal anatomy with variants of both pancreatic and biliary tree precede the chapters on pathological conditions. Clinical details, radiographs and their interpretation are restricted to one or two pages per case and are generally most informative. The examples selected come largely from the author's own collection and this is therefore a highly personal account of the subject.

Considering the cost of the book, however, too many of the radiographs are either hazy or the details in them are obscured by excess contrast material. The examples of the normal pancreatogram and biliary tree are good with many lateral views to show extra detail. Pseudocysts are covered to excess, even though the authors warn repeatedly against pseudocyst filling because of the risks of sepsis. The difficulty of distinguishing between pancreatic cancer and pancreatitis is not sufficiently emphasized in the introduction to these sections, although the authors freely admit their own confusion in the legends to the many examples given and they further stress the value of clinical information for correct interpretation of radiographs.

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east Cancer—Advances in Research

Edited William L. McGuire. 227×15
Illustrated. 1978. Edinburgh: Churchill L

THIS, the first of a series of books to be e
McGuire, in which it is hoped to present
us aspects of breast cancer, is concern
s of treatment and includes reviews
chemotherapy, endocrine tre nent and
e selected authors are master of th r su
orities; although much information
sed them elsewhere, its gathering together
volume will save considerable time and effort for th
who wishes to keep abreast of modern developments. There is also a comprehensive account of the pathology of the disease and its relationship to its natural history, written by Dr Edwin Fisher.

Quite apart from the practising clinician, there is a considerable content of fundamental knowledge which will interest the clinical investigator. Dr McGuire's own chapter on endocrine therapy is a good example; it is a masterly account of the fundamental as well as the therapeutic principles involved. He is to be congratulated on his initiative in producing what should be a very useful series of books. If the standard of succeeding volumes is up to this first one, the series will be a valuable aid to those interested in this common disease.

A. P. M. FORREST

Aspiration Cytology of the Breast

Hubert Schöndorf (translated by Volker Schneider). 245×170 mm. Pp 141+vii. 1978. Eastbourne: Holt–Saunders. £18·25.

ASPIRATION cytology for the diagnosis of breast lumps is practised more frequently in Europe and in Scandinavia than in Britain. This small book, with clearly written and concise text, and beautifully reproduced illustrations, details the method and provides a reference atlas for the interpretation of smears. Not that the diagnosis of breast smears can be learnt from a book. As cell detail is often lost, one must rely on nuclear characteristics, considerable skill and experience.

The author recommends that a solid discrete lesion can safely be left in the breast provided mammography and needle aspiration cytology do not provide evidence of malignancy. In our hands, needle aspiration is used to differentiate cystic from solid lesions, to treat cysts and to provide a provisional diagnosis based on cytology of the nature of a solid lesion; but we adhere to standard British practice and would still recommend that all palpable solid lesions are surgically removed.

Another interesting difference from British tradition is the origin of this book in a department of gynaecology; in many centres in Germany, breast disease is treated by a gynaecologist rather than a general surgeon.

This small book is very expensive but it is of value to those who are interested in this diagnostic technique.

A. P. M. FORREST

English for Doctors and Nurses

Joy Parkinson. 215×140 mm. Pp. 124, with 8 illustrations. 1978. London: Evans. £1·95.

THINK I write moderately good and clear English although a
of my friends, and many less favourably disposed, say I
e matters convoluted and obscure. Be this as it may, I get

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interest ce. le ur y b . The major
discussion to t urethra and ad ne mechanisms.
Great emp a is laid on the pla of ureth scopy using
carbon dioxide in making an accurate assessment of the problems, and there are many line drawings on the endoscopic appearances of the bladder neck.

I think most urologists involved in female urological problems, especially incontinence, take more note of videocystographic appearances of the bladder neck and urethra rather than endoscopic views. There is a good chapter on diseases of the urethra with a good account of urethral diverticulae, and bladder drainage is dealt with adequately. There is much useful information in the book, but certain topics are dealt with very inadequately, and I think the treatment of the vesicovaginal fistula could be elaborated. The importance of bladder instability in urinary incontinence is emphasized, and techniques of investigation and treatment discussed.

This book can be recommended to gynaecologists who are new to this field, but I doubt that urologists would find the depth of discussion adequate.

P. H. L. WORTH

Medical Acid–Base Balance: The Basic Principles

Michael L. G. Gardner. 235×155 mm. Pp. 125, with 37 illustrations. 1978. London: Baillière Tindall. £3·95.

THIS small book is a straightforward, clearly written account of a subject which many clinicians find confusing. It is aimed
primarily at undergraduate medical studer both preclinical
and clinical, but the author hopes that it so be ful to
clinicians for revision purposes, and to es f gher
qualifications in anaesthetics. The pr t ject
is entirely orthodox, but in the explana ods
for quantifying acid–base balance it il
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216 [illegible] about [illegible] illustrations. Approx. UK net price £8·5

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42–44 Triangle West, Bristol BS8 1EX

ACHALASIA OF THE CARDIA

H. R. S. HARLEY, MS, FRCS, *Consultant Cardiothoracic Surgeon, Llandough Hospital, Penarth, Glamorgan.*

Contents: Morbid Anatomy and Histology; Aetiology; Clinical Features; Radiological Examination; Oesophagoscopy; Carcinoma of the Oesophagus; Respiratory Complications; Joint Complications; Surgical Treatment; Results of the Modified Heller's Operation; References; Index.

In this book coverage of the physiological and radiological abnormalities of the oesophagus is given, differential diagnosis is discussed at length and the importance of motility studies to a proper understanding of this and other diseases of the oesophagus is stressed. Whilst this book is concerned primarily with achalasia of the cardia, upsets of motility of the oesophagus due to other causes, such as diffuse oesophageal sp[illegible] presbyoesophagus, reflex oesophagitis and progressive systemic sclerosis, are g[illegible] careful consideration.

216 × 138 mm [illegible] pages, 83 illustrations. UK net price £10·00

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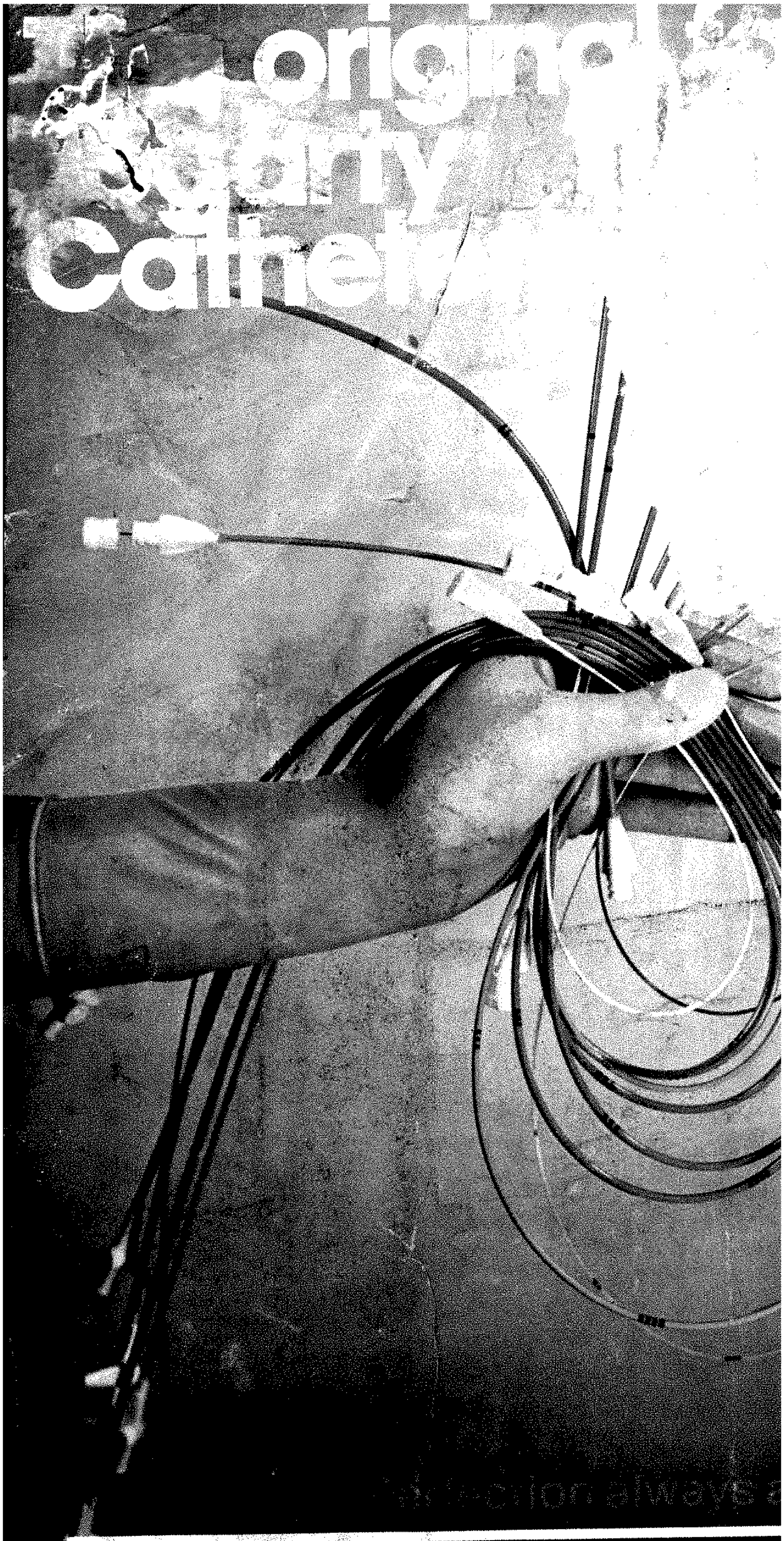

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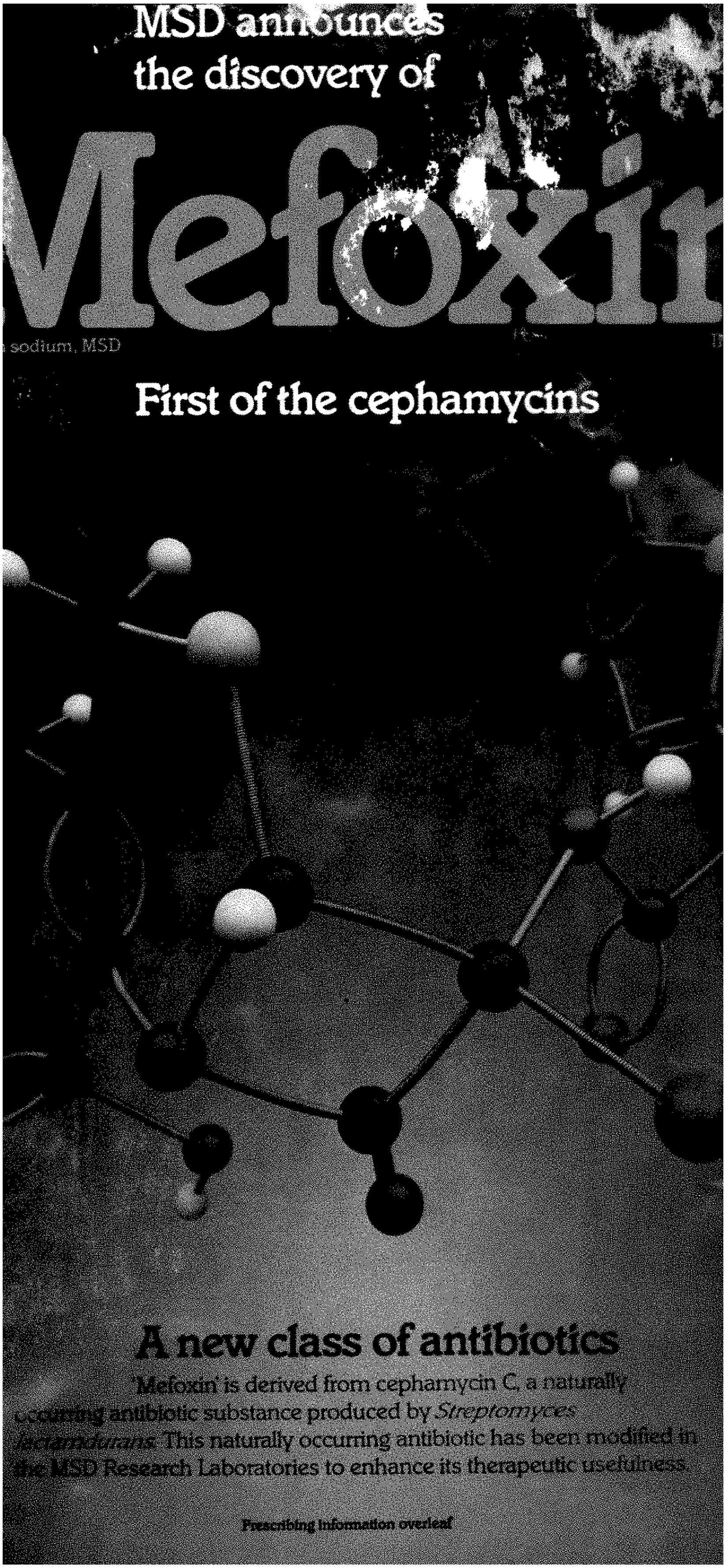

MSD announces
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Mefoxin

sodium, MSD

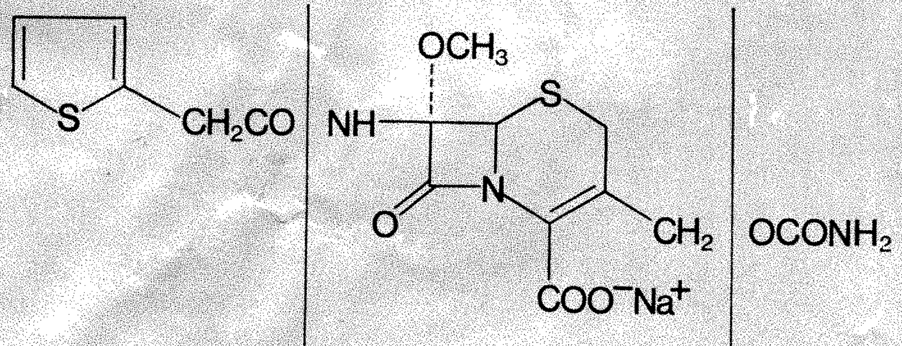
First of the cephamycins

A new class of antibiotics

'Mefoxin' is derived from cephamycin C, a naturally occurring antibiotic substance produced by *Streptomyces lactamdurans*. This naturally occurring antibiotic has been modified in the MSD Research Laboratories to enhance its therapeutic usefulness.

Prescribing information overleaf

[illegible] que molecular structure offering [illegible] clinical benefits and a specific clinical profile.



Thienylacetyl side-chain:
enhances activity against Gram-positive pathogens

Cephamycin nucleus:
provides bactericidal activity against a wide range of pathogens, Gram-negative in particular. 7α-methoxy group protects against β-lactamase degradation

Carbamoyloxy side-chain:
protects antibiotic from being metabolised

▼Prescribing information

Indications
'Mefoxin' is a broad-spectrum bactericidal antibiotic indicated for the treatment of infections caused by susceptible strains of Gram-positive and Gram-negative pathogens both aerobic and anaerobic.

'Mefoxin' has been clinically effective not only in infections due to antibiotic-sensitive organisms, but also in infections due to organisms resistant to one or more of the following antibacterial agents: penicillin, ampicillin, carbenicillin, tetracyclines, erythromycin, chloramphenicol, cephalosporins, kanamycin, gentamicin, tobramycin, and sulphamethoxazole-trimethoprim.

Many Gram-negative pathogens are resistant to penicillins and cephalosporins through the action of the β-lactamases which are produced by these pathogens. 'Mefoxin' is remarkably stable in the presence of these bacterial β-lactamases, both penicillinases and cephalosporinases. Hence, the clinical efficacy of 'Mefoxin' extends to many infections caused by such pathogens.

'Mefoxin' is indicated for the treatment of the following infections caused by sensitive bacteria:
peritonitis and other intra-abdominal and intrapelvic infections; female genital tract infections; septicaemia; urinary tract infections; respiratory tract infections; bone and joint infections; and skin and soft-tissue infections.

'Mefoxin' is indicated for adjunctive therapy in the surgical treatment of infections, including abscesses, infection complicating hollow visceral perforations, cutaneous infections, and infections of serous surfaces, whether caused by aerobes, mixed aerobes and anaerobes, or anaerobes.

icrobiology
'Mefoxin' is active *in vitro* against:
erobic bacteria
ram-positive cocci including: Staphylococci: (including coagulase-positive, coagulase-negative, and penicillinase-producing strains); Group A beta-haemolytic streptococci *(Streptococcus yogenes);* Group B beta-haemolytic streptococci *(Streptococcus galactiae); Streptococcus pneumoniae (Diplococcus pneumoniae);* other streptococci (except group D streptococci including enterococci, most strains of which are resistant, e.g. *Streptococcus faecalis). Gram-negative cocci* including: *Neisseria gonorrhoeae* (including penicillinase-producing strains); *Neisseria meningitidis. Gram-negative rods (facultative anaerobes)* including: *Escherichia coli; Klebsiella pneumoniae;* Klebsiella spp.; *Proteus mirabilis.* *Proteus* (indole-positive): *Proteus vulgaris; Proteus rettgeri; Proteus morganii; Haemophilus influenzae; Serratia marcescens;* Providencia spp.; Salmonella and Shigella spp.

Anaerobic bacteria
Gram-positive cocci including: Peptococcus spp.; Peptostreptococcus spp.; Micro-aerophilic streptococcus. *Gram-positive rods including: Clostridium perfringens;* Clostridium spp.; Eubacterium spp.; *Propionibacterium acnes. Gram-negative cocci including:* Veillonella spp. *Gram-negative rods including: Bacteroides fragilis; Bacteroides melaninogenicus;* Bacteroides spp. (including both penicillin-susceptible and penicillin-resistant strains); Fusobacterium spp.

'Mefoxin' is active against some strains of the following bacteria: *Acinetobacter calcoaceticus var. anitratum (Herellea vaginicola); Acinetobacter calcoaceticus var. lwoffi (Mima polymorpha); Alcaligenes faecalis;* Citrobacter spp. and Flavo-bacterium spp.; Enterobacter spp.

'Mefoxin' is not active against Pseudomonas, most strains of enterococci and many strains of *Enterobacter cloacae.*

Dosage and administration
'Mefoxin' may be administered intravenously or intramuscularly. (See reconstitution directions for each route below.) Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organisms, and condition of the patient.

Therapy may be started while awaiting the results of susceptibility testing.

Dosage: The usual adult dosage is 1 g or 2 g of 'Mefoxin' every eight hours. (See chart.)

In adults with renal insufficiency, an initial loading dose of 1 g or 2 g may be given. After a loading dose, the following recommendations for *maintenance dosage* may be used as a guide.

Usual adult dosage

Type of infection	Dose	Frequency	Total daily dosage
Uncomplicated	1 g	Every 8 hours (occasionally every 6 hours)	3 g (4 g)
Moderately severe or severe	2 g	Every 8 hours (occasionally every 6 hours)	6 g (8 g)
Infections generally needing antibiotics in higher dosage	3 g (2 g)	Every 6 hours (Every 4 hours)	12 g

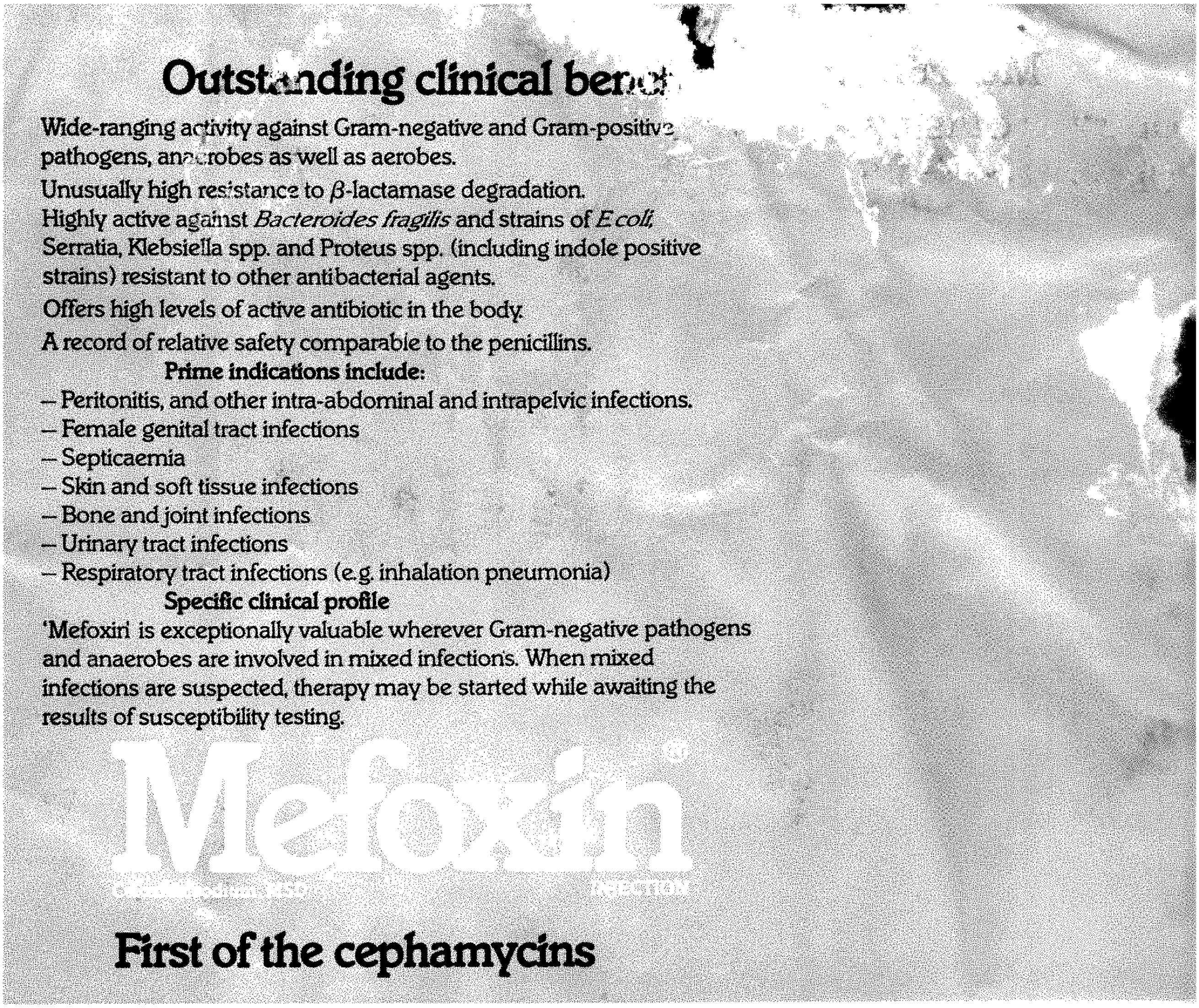
Maintenance dosage of 'Mefoxin' in adults with reduced renal function

Renal function	Creatinine clearance (ml min)	Dose	Frequency
Mild impairment	50-30	1-2 g	Every 8-12 hours
Moderate impairment	29-10	1-2 g	Every 12-24 hours
Severe impairment	9-5	0.5-1 g	Every 12-24 hours
Essentially no function	<5	0.5-1 g	Every 24-48 hours

In the patients undergoing haemodialysis, the loading dose of 1 to 2 g should be given after each haemodialysis, and the maintenance dose should be given as indicated in the table above.

Intravenous administration: reconstitute 'Mefoxin' with Water for Injection BP: 1 g is soluble in 2 ml. Although 'Mefoxin' is very soluble, for intravenous use it is preferable to add 10 ml of Water for Injection BP to the 1 g vial or the 2 g vial. Shake to dissolve and then withdraw entire contents of vial into syringe.

For direct intravenous injection, 'Mefoxin' may be slowly injected into



Outstanding clinical benefit

Wide-ranging activity against Gram-negative and Gram-positive pathogens, anaerobes as well as aerobes.

Unusually high resistance to β-lactamase degradation.

Highly active against *Bacteroides fragilis* and strains of *E.coli*, Serratia, Klebsiella spp. and Proteus spp. (including indole positive strains) resistant to other antibacterial agents.

Offers high levels of active antibiotic in the body.

A record of relative safety comparable to the penicillins.

Prime indications include:

– Peritonitis, and other intra-abdominal and intrapelvic infections.
– Female genital tract infections
– Septicaemia
– Skin and soft tissue infections
– Bone and joint infections
– Urinary tract infections
– Respiratory tract infections (e.g. inhalation pneumonia)

Specific clinical profile

'Mefoxin' is exceptionally valuable wherever Gram-negative pathogens and anaerobes are involved in mixed infections. When mixed infections are suspected, therapy may be started while awaiting the results of susceptibility testing.

Mefoxin®
[illegible] sodium, MSD INJECTION

First of the cephamycins

the vein over a period of 3 to 5 minutes or may be given through the tubing when the patient is receiving parenteral solutions.

An intermittent intravenous infusion of 'Mefoxin' may be employed when large amounts of fluid are to be given. However, during infusion of the solution containing 'Mefoxin', it may be advisable temporarily to discontinue administration of any other infusion solution at the same site (by using an appropriate IV infusion set).

A solution of 'Mefoxin' may also be given by continuous intravenous infusion (see below for compatibility and stability).

Intramuscular administration ONLY
Reconstitute 'Mefoxin' 1 g with 2 ml of Water for Injection BP, or 0.5% or 1% lignocaine hydrochloride (without adrenaline) solution. 'Mefoxin' is given by deep injection into a large muscle mass. Avoid injection into a blood vessel.

Compatibility and stability
A solution of 'Mefoxin' in Water for Injection BP may be added to the following solutions. 0.9% Sodium Chloride Injection BP, 5% or 10% Dextrose Injection BP, Dextrose and Sodium Chloride Injection (5%/0.9%, 5%/0.45%, or 4.3%/0.18%), Lactated Ringer's Injection USP, 5% Dextrose in Lactated Ringer's Injection, 5% or 10% invert sugar in water, 10% invert sugar in saline solution, 4.2% Sodium Bicarbonate Injection BP, M/6 Sodium Lactate Injection BP.

'Mefoxin', as constituted to 1 g/10 ml with Water for Injection BP, Water for Injection BP preserved with parabens or benzyl alcohol, 0.9% Sodium Chloride Injection BP, or 5% Dextrose Injection BP, maintains satisfactory potency for 24 hours at room temperature, for 96 hours under refrigeration, and for 13 weeks in the frozen state.

'Mefoxin' can be administered concomitantly with such antibiotics as gentamicin, tobramycin, carbenicillin or amikacin. When 'Mefoxin' is administered with another antibiotic, they should not be mixed in the same syringe.

Contra-indications
'Mefoxin' is contra-indicated in persons who have shown hypersensitivity to cefoxitin. In the absence of clinical experience, 'Mefoxin' should not be administered to patients who have shown hypersensitivity to cephalosporins.

Precautions
There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and other β-lactam antibiotics, penicillins, and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most β-lactam antibiotics.

Before therapy with 'Mefoxin', careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibiotics. 'Mefoxin' should be given cautiously to penicillin-allergic patients.

Any patient who has demonstrated some form of allergy particularly to drugs, should receive antibiotics cautiously. If an allergic reaction to 'Mefoxin' occurs, the drug should be discontinued.

The total daily dosage should be reduced when 'Mefoxin' is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see 'Dosage and administration') because high and prolonged serum antibiotic concentrations can occur from usual doses.

Interference with laboratory tests
A false-positive reaction to glucose in the urine may occur with reducing substances but not with the use of specific glucose oxidase methods.

Use in pregnancy
Use of the drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the foetus due to 'Mefoxin'. There are no controlled studies with 'Mefoxin' in pregnant women.

Nursing mothers
'Mefoxin' is excreted in human milk.

Infants and children
Pending the outcome of clinical trials in progress, the conditions for use of 'Mefoxin' in infants and children remain to be defined.

Side effects
'Mefoxin' is generally well tolerated. Side effects rarely require stopping treatment and usually have been [illegible].

Local reactions
Thrombophlebitis has occurred with [illegible]. Pain induration and tenderness after [illegible] have been reported.

Allergic
Maculopapular rash urticaria pruritus [illegible] other allergic reactions have been noted rarely.

Gastro-intestinal
Diarrhoea has been reported rarely.

Blood
Transient leucopenia and neutropenia [illegible]. Some individuals particularly those with azotaemia [illegible] positive direct Coombs tests during therapy with [illegible].

Liver function
Transient elevations in SGOT SGPT [illegible] alkaline phosphatase have been reported rarely.

Kidney
Elevations in serum creatinine and or [illegible] have been observed. The role of 'Mefoxin' in changes in renal function tests is difficult to assess since factors predisposing to [illegible] azotaemia or to impaired renal function usually have been present.

Presentation
In vials containing 1 g or 2 g of cefoxitin as the sodium salt. Each gram of cefoxitin contains approximately [illegible] sodium.

Product licence numbers: 1 g 0025/0134 2 g [illegible]

Product authorisation numbers: 1 g PA 35/40/1 [illegible] 35/40/2

Issued October 1978

Additional information is available to the medical profession on request.

Basic NHS cost is £4.47 for the 1 g vial, and [illegible] for the 2 g vial.

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A comparison between disposable and no[illegible]ispo suction drainage units: a report of a contr[illegible] tri

B. J. BRITTON, O. J. A. GILMORE, J. S. P. LUMLEY AND W. M. CAS[illegible]

SUMMARY

A randomized trial of high vacuum Redivac drains and low vacuum Portovac drains has been conducted in 46 female patients undergoing simple mastectomy through a transverse skin incision. The Redivac units drained less fluid, stayed in place for a day less than the Portovac units and were emptied once less often.

DRAINAGE of surgical wounds is a long established surgical practice. It has, however, been subjected to relatively few clinical trials. Furthermore, a prospective study of over 20 000 wounds demonstrated that open drains increase the overall infection rate and require a great deal of nursing time, although they do reduce the incidence of intra-abdominal sepsis (Cruse and Foord, 1973). The introduction of suction drainage (Murphey, 1947) and, later, the evacuated glass bottle (Redon, 1955) offered new opportunities, and there is now evidence that this closed vacuum system has significant advantages in mastectomy wounds (Morris, 1973; Bourke et al., 1976). The desire for single-use disposable appliances has led to the introduction of plastic low vacuum drainage units, but these have several theoretically undesirable features (Lumley et al., 1974). We have therefore conducted a randomized clinical trial to compare the high vacuum Redivac system against the low vacuum Portovac drainage unit in surgical patients.

Patients and methods

Only female patients undergoing simple mastectomy without axillary clearance were eligible for the trial. Patients were randomly allocated at the end of the operation according to instructions revealed in a numbered enevelope labelled R for Redivac (Zimmer Orthopaedic Ltd) or P for Portovac (Howmedica UK Ltd). The operations were all performed in a similar manner by four surgeons using transverse skin incisions. Subcutaneous sutures were not used and the skin was closed with interrupted 3/0 black silk mattress stitches. Two perforated tubes were used, one placed along the base of the lower skin flap, the other in the axilla. Both tubes were connected to one suction bottle. The wound was dressed with a sterile adhesive dressing without pressure. Several variables of potential importance such as the length of the skin incision, the presence of tension in the flaps and the cup size of the patient's brassière were also recorded.

After the operation no restrictions were placed on movement of the arm and the drains were emptied or changed as follows. Both systems were only touched either when they were full or when the vacuum had expired. In the case of the Redivac a completely new sterile evacuated bottle was then connected whilst in the case of the Portovac, fluid was drained out, the bellows compressed and the drain plug replaced. Each time a drain was changed or emptied the contained fluid was measured and sent for culture. All drains were removed when the drainage volume in a 24-h period was less than 25 ml. At this time the tips of the perforated tubes, a swab of the drain site and the contents of the containers were all sent for culture.

Wounds were inspected for infection, necrosis, breakdown and fluid under the flaps on the fifth, seventh and ninth postoperative days. Any wound discharge was swabbed and cultured and wounds were classified as either clean or infected. Infection was diagnosed if (*a*) at any time a purulent discharge occurred or (*b*) a profuse growth of an organism was obtained from the swab of a serous discharge. Necrosis or breakdown occurred if a length of wound greater than 1 cm necrosed or separated. Other objective criteria of wound healing such as the time of suture removal and the day of discharge from hospital were noted as well as the presence or aspiration of fluid from beneath the skin flaps. Administration of antibiotics was avoided both before and after operation. Statistical comparisons between the two groups were made using either Student's t test or the χ^2 test for 2×2 tables.

Table I: COMPARISON OF THE PHYSICAL CHARACTERISTICS OF THE PORTOVAC AND REDIVAC GROUPS

	Portavac ($n = 24$)	Redivac ($n = 22$)	P
Age (yr) mean ± s.e. mean)	57 + 3	49 ± 3	$P < 0.03$
Brassière cup size (A, B or C)	6A, 9B, 9C	3A, 17B, 1C*	$P < 0.01$
Incision length (cm)	26 ± 1	24 ± 1	n.s.
Thin flaps	9	10	n.s.
Pectoral fascia removed			
Partial	14	11	n.s.
Complete	5	4	
Not known	5	7	
Tension of flaps	3	6	n.s.
Duration of operation (min mean ± s.e. mean)	63 ± 6	59 ± 9	n.s.
Antibiotics before operation	0	1	n.s.
Antibiotics after operation	3	0	n.s.

* One cup size not recorded.

Table II: RESULTS COMPARING THE TWO GROUPS DRAINED BY EITHER THE PORTOVAC OR REDIVAC DRAIN

	Portovac ($n = 24$)	Redivac ($n = 22$)	P
Number of times drain emptied (mean ± s.e. mean)	2·5 ± 0·3	1·4 ± 0·3	$P < 0.01$
Total volume drained (ml mean ± s.e. mean)	332 ± 53	187 ± 24	$P < 0.01$
Drain in place (d mean ± s.e. mean)	5·8 ± 0·3	4·7 ± 0·2	$P < 0.005$
Wound infection	6	2	n.s.
Necrosis and breakdown	6	5	n.s.
Aspiration required	1	1	n.s.
Length of stay in hospital (d mean ± s.e. mean)	11·7 ± 1·1	9·9 ± 0·6	n.s.

Results

Twenty-four wounds were drained using the Portovac bottle whilst 22 patients received the Redivac drain. The physical characteristics of the two groups are shown in *Table I*: they were reasonably well matched,

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[illegible] rs of [illegible] tween [illegible] all breas [illegible] tainer drain [illegible] as 145 ml in [illegible] the Redivac group. [illegible] drains [illegible] o emptied at least once [illegible] and [illegible] in place longer, on average by about a day (*Table II*). There was no significant difference in the number of positive cultures from fluid, bottles or drain tips. Clinically 6 wounds became infected in the Portovac group and 2 in the Redivac group. Necrosis and breakdown occurred in 6 and 5 patients respectively whilst 1 patient in each group required aspiration. Of the 6 clinically infected wounds in the Portovac group, 4 were associated with necrosis and breakdown of the wound. In addition, 2 wounds became infected without necrosis and 2 wounds necrosed without infection. In the Redivac group 2 wounds developed infection without necrosis and 5 wounds necrosed without infection.

Patients in the Portovac group stayed in hospital about 2 days longer than those in the Redivac group but this was not statistically significant (*Table II*).

Discussion

In our laboratory study (Lumley et al., 1974) we assumed that the disposable type drains with a lower vacuum would require more frequent emptying. We demonstrated that one consequence of this was an increased liability to infection within the system which could then spread retrogradely on re-evacuation. Clinically we have shown that the Portovac drain did require more frequent emptying, drained a greater volume of fluid and needed to remain in place longer. However, this did not result in a greater incidence of positive cultures from either the bottle contents or the drain tips. The incidence of clinical wound infection in the Portovac group was, however, greater than in the Redivac group but 4 of the 6 infections were associated with necrosis of the skin edges. Overall 14 of the 46 patients in this series developed either infection or necrosis of the wound. Mastectomy, with its large skin flaps, is usually associated with a high incidence of wound problems, which may occur in up to 2 out of every 5 patients following a radical mastectomy (Zintel and Nay, 1964). Although the Redivac drain has been associated with necrosis of skin (McCallum, 1961), this was probably in cases where very thin skin flaps were used and, in general, [illegible] n necrosis is more likely to be related to surgical chnique and the thickness and tension of the skin aps (Heald, 1973) rather than to the type of drain. he slightly greater average age of the patients in the ortovac group might also have contributed to the ncidence of skin necrosis, but this is unlikely to have [illegible] a major effect. Whilst the unbreakable nature of disposable drains is an advantage, the fact that [illegible] be completely emptied of fluid is a nuisance [illegible] ore, the Portovac drain is occasionally [illegible] vacuate and close singlehanded. In [illegible] patients with Portovac drains extra [illegible] be inserted into the closed incision [illegible] through the wound into the system. [illegible] f the Redivac drain therefore appear [illegible] its greater vacuum, which rapidly eliminates any dead space and approximates the skin flaps together and to the chest wall, thereby encouraging healing, reducing drainage and thus hospital inpatient stay.

Acknowledgements

We are extremely grateful to Mr L. P. Thomas, Mr D. E. Sturdy, Mr R. A. Payne and Professor G. W. Taylor for allowing us to study patients admitted under their care. We are grateful to Howmedica (UK) Ltd for supplying the Portovac drains.

References

BOURKE J. B., BALFOUR T. W., HARDCASTLE J. D. et al. (1976) A comparison between suction and corrugated drainage after simple mastectomy; a report of a controlled trial. *Br. J. Surg.* **63**, 67–69.

CRUSE P. J. E. and FOORD R. (1973) A five-year prospective study of 23,649 surgical wounds. *Arch. Surg.* **107**, 206–210.

HEALD R. J. (1973) Suction drainage in breast surgery. *Br. Med. J.* **3**, 232.

LUMLEY J. S. P., BRITTON B. J. and CHATTOPADHYAY B. (1974) The physical and bacteriological properties of disposable and non-disposable suction drainage units in the laboratory. *Br. J. Surg.* **61**, 832–837.

MCCALLUM G. T. (1961) Some hazards of suction drainage of large skin flaps. *Ann. Surg.* **154**, 990–992.

MORRIS A. M. (1973) A controlled trial of closed wound suction drainage in mastectomy. *Br. J. Surg.* **60**, 357–359.

MURPHEY D. R. (1947) The use of atmospheric pressure in obliterating axillary dead space following radical mastectomy. *South. Surgeon* **13**, 372–375.

REDON H. (1955) La fermature des plaies étendues sous dépression. *Presse Med.* **63**, 1034.

ZINTEL H. A. and NAY H. R. (1964) Postoperative complications of radical mastectomy. *Surg. Clin. North Am.* **44**, 313–323.

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Hypertrophic scarring [illegible] De[illegible] [illegible]s [illegible]u[illegible] randomized trial

J. E. P. SIMPSON, M. ORNSTEI[illegible] C. [illegible] ND A [illegible]

SUMMARY

In a randomized prospective trial of thr[illegible] skin suture an increased inciden[illegible] o[illegible] scarring in paramedian and ingui[illegible] w[illegible] found to be associated with the use [illegible]f 2[illegible] subcuticularly. However, the variance the type of suture was less than that as sex of the patient. The patient's opin[illegible] ance of the scar was the same [illegible]or methods used in skin closure.

DEXON is a synthetic, absorbable suture made by the polymerization of glycolic acid (PGA). The tensile strength, knotting properties and handling characteristics (Hermann et al., 1970; Katz and Turner, 1971) have been found to be satisfactory and surgeons from several specialties have used the material successfully in clinical practice (Dardik et al., 1971; Alveryd and Jacobson, 1975). In 1975, Clough and Alexander-Williams reported the use of Dexon subcuticularly in wound closure at a time when we found, from a retrospective review, an increased incidence of hypertrophic scar formation (Cox and Simpson, 1975). We now report a randomized prospective trial on the incidence of hypertrophy in abdominal wound healing and on whether the type or position of the suture material is important in the production of scarring. Fourteen other possible aetiological factors have been studied and a symptomatic inquiry made.

Patients and methods

Three methods of skin closure have been compared in inguinal and paramedian wounds: subcuticular 2/0 PGA suture, subcuticular 0 nylon suture and transverse interrupted 0 nylon sutures. A consecutive series of 152 patients undergoing surgery for inguinal hernia, gallstone disease or benign peptic ulceration gave informed consent to be randomly allocated to one of the three skin closure groups with or without a plastic spray dressing. Patients admitted to the trial were grouped by sex, age (under and over 50) and site of incision before randomization. The deep layers of all wounds were closed identically with continuous chromic catgut to the peritoneum or external oblique aponeurosis and continuous monofilament nylon to the rectus sheath.

A form was completed for each patient, recording the length and depth of the wound, the site and nature of any discharge, the surgeon, the duration of operation and the date of suture removal. Height, weight, girth and haemoglobin and plasma protein concentrations were also recorded. A note was made of the patient's reaction to the wound and of any particular symptoms such as itching. Measurements of the wound were made at 3 weeks, 3, 6 and 12 months after surgery. The width of the scar was measured with a calliper and an attempt then made to compress the tissue between the points placed on the edges of the scars. Scars were said to be hypertrophied when they were raised above the surrounding skin, and incompressible when the points of the calliper could not be brought together.

The data were analysed by a standard method described by Armitage (1971). The results were expressed as parameters for the main factors influencing the proportion of hypertrophied wounds. Each parameter represents the change in the natural logarithm of the odds on hypertrophy being caused by the corresponding factor. One level of each factor was absorbed into the general mean and did not appear in the analysis.

[illegible] I [illegible]ATIENT CHAR[illegible]TERIS[illegible] [illegible]E S[illegible]RE GROUPS

	Subcuticular PGA	Subcuticular nylon	[illegible] nylon
No. of patients	48	40	45
Mean age (yr)	51±13	51±12	47
Male/female	28/20	22/18	28/17
Mean girth (cm)			
Male	89	89	89
Female	85	80	82
Mean Hb (g/dl)			
Male	14·9	14·4	14·9
Female	13·3	13·6	13·2
Mean albumin (g/l)			
Male	41	43	42
Female	40	38	43
Operation by			
Consultant	8	7	8
Registrar	21	18	23
SHO	19	15	14

Table II: NUMBER AND PERCENTAGE OF PATIENTS WITH HYPERTROPHIC SCARS

	Suture type								
	Subcuticular PGA			Subcuticular nylon			Interrupted nylon		
		Hypertrophy			Hypertrophy			Hypertrophy	
Incision	No.	No.	%	No.	No.	%	No.	No.	%
Paramedian	26	19	73	25	14	56	25	13	52
Inguinal	22	4	18	15	1	7	20	3	15
Total	48	23	47	40	15	37	45	16	35

Table III: DISTRIBUTION OF PATIENTS AND SCARS SHOWING HYPERTROPHY BY SEX, AGE AND SITE OF INCISION

	Inguinal			
	Male		Female	
	<50 yr	50 yr +	<50 yr	50 yr +
PGA	7 (3)	15 (1)	0	0
Subcuticular nylon	6 (0)	9 (1)	0	0
Interrupted nylon	7 (2)	13 (1)	0	0
Total	20 (5)	37 (3)	0	0

	Paramedian			
	Male		Female	
	<50 yr	50 yr +	<50 yr	50 yr +
PGA	2 (1)	4 (1)	9 (8)	11 (9)
Subcuticular nylon	2 (2)	5 (1)	9 (4)	9 (7)
Interrupted nylon	5 (1)	3 (0)	9 (7)	8 (5)
Total	9 (4)	12 (2)	27 (19)	28 (21)

Figures represent the number of patients in that group, with the number of scars that developed hypertrophy given in brackets.

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Correspondence to: A. G. Cox, Northwick Park Hospital, Watford Road, Harrow.

[illegible] ts (67 per cent) [illegible] moved away from the [illegible] and the hospital. One [illegible] carcinoma, 4 [illegible] se at the time of surgery [illegible] dehiscence. Characteristics of the [illegible] of the three groups are recorded in *Table I* and show that the groups are comparable.

Fifty-four patients (41 per cent) had hypertrophic scar formation, which was often segmental. The hypertrophy affected over two-thirds of the wounds 18 patients and less than one-third in 10. The worst example of hypertrophy was in a paramedian wound which was a 10-mm wide, half cylinder of incompressible purplish-pink tissue; more commonly hypertrophic segments were 3 or 4 mm wide, compressible by 1 or 2 mm and pink in colour. Hypertrophy was only rarely seen at the 3-week inspection but was usually apparent by 3 months if it was going to occur. Once formed, it changed little throughout the year of observation, except in 5 patients in whom it began to soften.

Use of spray as a wound dressing did not affect the incidence of hypertrophy, nor did the hypertrophy become aggressive, as in keloid scar formation. Twenty-three of the 48 wounds (47 per cent) closed with subcuticular PGA suture showed hypertrophy (*Table II*), an incidence significantly in excess of that seen with subcuticular nylon (37 per cent) ($P \sim 0{\cdot}04$ in a one-tailed t test). This hypertrophy was not dependent on the position of the suture material, since the incidence of hypertrophy was similar for nylon used subcuticularly (37 per cent) and as an interrupted suture (35 per cent). Therefore, the results for the two types of nylon suture were combined in the parametric analysis so that the standard errors were as follows: general mean, $0{\cdot}437 \pm 0{\cdot}392$; sex (male) $-1{\cdot}888 \pm 0{\cdot}583$; suture (PGA), $0{\cdot}795 \pm 0{\cdot}463$; incision (inguinal) $-0{\cdot}968 \pm 0{\cdot}632$; age (50) $0{\cdot}623 \pm 0{\cdot}440$.

The effect of sex is highly significant ($P < 0{\cdot}001$), the incidence of hypertrophy in females (72 per cent) far exceeding that in males (18 per cent) whichever form of wound closure was used. Even when paramedian wounds alone are considered the male incidence rises to 29 per cent (*Table III*). Patients under 50 (50 per cent) were more often affected than those who were older (34 per cent) but this did not reach significance at the 5 per cent level. Nor did the apparently large difference in incidence between the paramedian (60 per cent) and inguinal (14 per cent) wounds reach statistical significance when the other factors were taken into account. The residual χ^2 (deviance) was 5·429 with seven degrees of freedom, indicating that the model gives a good fit to the data.

No association was found between the presence of hypertrophy and the individual surgeon, the time taken to perform the operation, the use of a spray dressing, the presence of discharge from the wound or such patient characteristics as girth, haemoglobin and plasma protein concentrations. Too few patients came from abroad for the effect of race to be studied.

Thirty-nine patients (30 per cent) told us of itching in the wound which on 29 occasions (54 per cent) was associated with hypertrophy; it was less troublesome when clothes made of nylon were avoided. A hypertrophic wound was particularly uncomfortable if it crossed the waistband or was subject to pressure or rubbing in other ways, but it was not painful of itself. Of those patients with hypertrophic scars, 14 were disappointed (32 per cent) and 1 was disgusted by the appearance; 6 (7 per cent) were disappointed even when there was no hypertrophy. There was no difference between the three suture groups in the degree of satisfaction with the appearance.

Discussion

The cosmetic quality of abdominal scars is less important to the general surgeon than dehiscence and herniation and, in a busy surgical outpatients department, the patient's opinion of the scar is rarely sought. We have found that after straightforward abdominal surgery one-third of the wounds will show some degree of hypertrophy irrespective of the suture used. This is in keeping with the recently published results of Arabi and Alexander-Williams (1978), but using a stratified randomization and a statistical analysis designed for such a multi-factorial situation, this risk is significantly increased if PGA is inserted subcuticularly to close the skin. However, we do agree with Jones and Shorey (1975) that PGA suture has advantages since 14 per cent of our patients said they were apprehensive of suture removal, and avoiding suture removal saves nursing time.

Although patients complained of the appearance of a hypertrophic scar and of itching, they found less pain than had been previously described (Crockett, 1964). Less expected was the excessive frequency of hypertrophic healing amongst women, for some studies have reported equality between the sexes (Ketchum et al., 1974). At a 5 per cent level of significance, this study failed to confirm either the expected increased incidence of hypertrophy amongst younger patients (Ketchum et al., 1974) or the effect of the location and direction of the skin incision (King and Salzman, 1970), although there were trends in the expected direction.

References

ALVERYD A. and JACOBSON S. I. (1975) Dexon for sutures and ligatures. *Acta Chir. Scand.* **141**, 256–258.

ARABI Y. and ALEXANDER-WILLIAMS J. (1978) Hypertrophic scarring after subcuticular polyglycolic acid suture. *Lancet* **1**, 724.

ARMITAGE P. (1971) *Statistical Methods in Medical Research*, 3rd ed. Oxford, Blackwell Scientific, pp. 362–394.

COX A. G. and SIMPSON J. E. P. (1975) Polyglycolic acid suture material in skin closure. *Lancet* **1**, 452.

CLOUGH J. V. and ALEXANDER-WILLIAMS J. (1975) Surgical and economic advantages of polyglycolic acid suture material in skin closure. *Lancet* **1**, 194–195.

CROCKETT D. J. (1964) Regional keloid susceptibility. *Br. J. Plast. Surg.* **17**, 245–253.

DARDIK H., DARDIK I. and LAUFMAN H. (1971) Clinical use of polyglycolic acid polymer as a new absorbable synthetic suture. *Am. J. Surg.* **121**, 656–660.

HERMANN J. B., KELLY R. J. and HIGGINS G. A. (1970) Polyglycolic acid sutures. *Arch. Surg.* **100**, 486–490.

JONES S. M. and SHOREY B. A. (1975) Polyglycolic acid suture in skin closure. *Lancet* **1**, 390.

KATZ A. and TURNER R. (1971) Evaluation of tensile and absorption properties of polyglycolic acid sutures. *J. Surg. Gynecol. Obstet.* **131**, 701–716.

KETCHUM L. D., COHEN I. K. and MASTERS F. W. (1974) Hypertrophic scars and keloids. *Plast. Reconstr. Surg.* **40**, 140–145.

KING G. D. and SALZMAN F. A. (1970) Keloid scars. *Surg. Clin. North Am.* **50**, 595–598.

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Necrotizing sialometaplasia of palate

RANES C. CHAKRAVORTY, TATSUO YONEYAMA AND

SUMMARY

A patient with necrotizing sialometaplasia of the hard palate was treated with wide resection on a biopsy diagnosis of carcinoma. The literature on this recently identified entity is reviewed and the characteristic clinical features, histopathology and ultrastructure are summarized. To the best of our knowledge, no ultrastructural study concerning this entity has been previously reported. Unless recognized early, an extensive resection might be done needlessly.

IN a paper published in 1973, Abrams et al. reported on 7 patients (seen over an 8-year period) with ulcerating lesions of the palate that were generally diagnosed as being cancer but were not. These authors did not find any previous reports of this entity and termed it 'necrotizing sialometaplasia'.

Case report

E. C., a 54-year-old black male, was seen in the surgical clinic for a slightly tender lesion on the left side of the hard palate. About 3 weeks earlier he had been examined by a physician for some palatopharyngeal discomfort but no specific anomaly was noted in the oral cavity or pharynx. The patient had since developed a progressive swelling in the left hard palate which was tender but not painful and which had ulcerated 3 days previously. The patient was a heavy smoker, an occasional user of alcohol and had no other significant medical history.

Intraoral examination showed an ulcerated area about 1·5 cm in diameter on the right side of the hard palate. The base was occupied by shaggy yellowish necrotic tissue and the margins were sharply demarcated, with a red halo about 0·5 cm wide (*Fig.* 1). The lesion was mildly tender. The rest of the oral cavity, larynx and pharynx were unremarkable. Neck nodes were not palpable. Routine physical and laboratory examination were within normal limits. The VDRL test was negative. Radiographs of the area showed mild b palatal process of the left maxilla.

A biopsy of the lesion was initially read as an ulcer and fresh tissue was requested. The second biopsy was interpreted as squamous cell carcinoma. Two days later, the ulcerated area was widely excised with frozen section control until the margins were through normal tissue. The bone of the palate was left intact.

Postoperative healing was satisfactory though slower than expected. The final report on the excised specimen under light microscopy was necrotizing sialometaplasia. The patient remains free of any local recurrence at 18 months.

Microscopic examination

The surgical specimen was a 1·5-cm round ulcer with a smooth margin and large area of ischaemic necrosis involving mucosa,

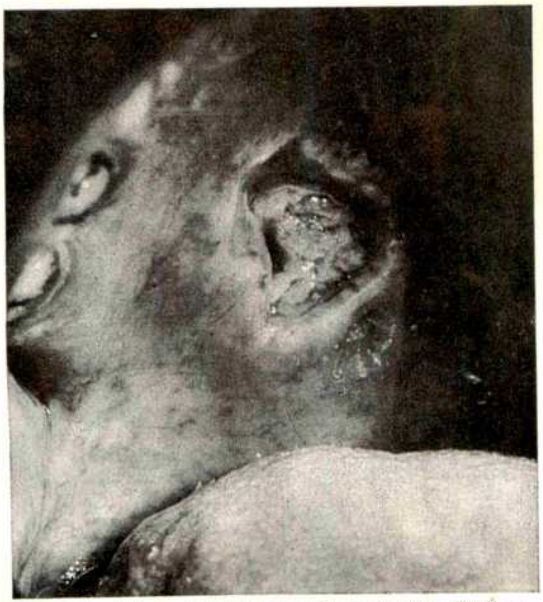

Fig. 1. The lesion, with sharp margins and a sloughy base.

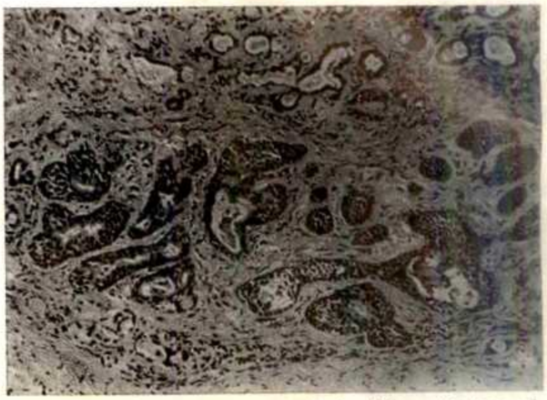

Fig. 2. Extensive squamous metaplasia of the epithelium of acini and ducts with infiltration of chronic inflammatory cells in the fibrous stoma. (HE. × 82.)

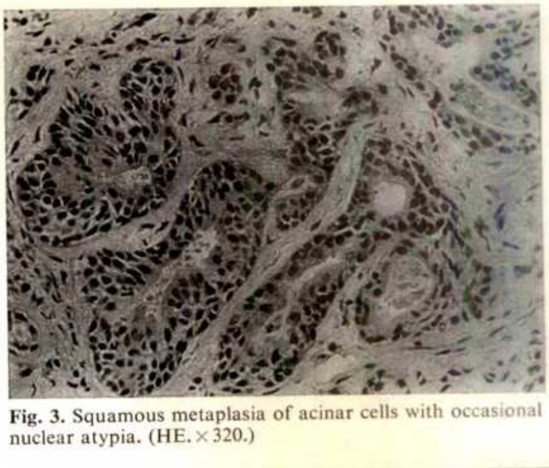

Fig. 3. Squamous metaplasia of acinar cells with occasional nuclear atypia. (HE. × 320.)

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eliomato
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ils with slight
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inor salivary glands. Multiple
ar ducts as well as many acini sh
sia of the lining epithelium (*Fig.* 2) wherea
tely obliterated by proliferating metaplastic
tain ducts showed a small lumen surrounde
quamous cells that displayed slight nuclea
mitotic figures and occasional areas o
small vessels were noted in the excise
e essentially unremarkable.
iopsy material from the lesion disclose
anges. The combination of pseudoepitheliomatou
plasia and nests of metaplastic squamous cells along with mucosal ulceration produced a picture mimicking well-differentiated infiltrating squamous cell carcinoma.

lectron microscopy

A gradual transition from relatively undisturbed acinar cells to metaplastic squamous epithelium was seen. The latter was evidenced by increased desmosomes, tonofibrils and retention of their secretory granules. Other intracytoplasmic organelles were not remarkable. The lateral borders of the canaliculi were also changing from loosely arranged microvilli, in the undisturbed cells, to a tight and relatively smooth border in the metaplastic cells. Occasional degenerating acinar cells revealed a single or coalescent degenerative vacuole, compressing the nucleus. Degenerative vacuoles were much less electron-dense than developing immature secretory granules and they were usually membrane-bound. Other structures, such as myoepithelial cells, basement membrane and blood vessels, were not emarkable. We did not observe any particulate matter uggesting a micro-organism as the possible aetiology of this disease.

Review of the literature

Since its initial description, about 30 patients afflicted with this disease have been reported in the literature. Males have predominated, with ages ranging between 18 (Pindborg and Harder, 1977) and 83 (Johnson, 1977). Clinical details are surprisingly vague and non-specific.

When documented, lesions have on occasion been painful. In most patients there had been at least a 3-week delay before medical attention was sought, testifying to the relative painlessness of the lesions. The use of tobacco has not always been documented though at least 2 patients had never smoked and some were teetotallers (Myers et al., 1975; Fechner, 1977). Our patient had a non-reactive VDRL test though one reported patient was known to have syphilis (Bannayan et al., 1976). The lesion was generally clearly to one or the other side of the midline though in a few instances bilateral lesions have been seen. At least 3 patients had a raised mass only without any ulceration. Significant cervical lymphadenopathy has not been recorded. Lesions biopsied were generally diagnosed as cancer (as was ours) and were thus treated by wide local excision except when the lesion spontaneously regressed because of patient delay. The benign and self-limiting nature of the lesion is evidenced by an 8-year follow-up of a patient who ven though the margins at sease.

aplasia of the palate is a self-
condition occurring in adults. No
ogical agents have been reported; we
er the electron microscope for microbial
ing this disease but the results were
ve. The fact that the disease occurs mainly in
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here is no clinical or
rt this hypothesis, how-
s being the necrotizing or
nic stomatitis (Philipsen et al.,
ined as it has been described
in non smokers. Moreover, identical changes have been described in the major salivary glands (Bhargava and Monga, 1975; Batsakis, 1976) and in the mucous glands of the nasal cavity (Maisel et al., 1976; Johnston, 1977). Probably the lesions represent compromised local blood supply with reactive squamous metaplasia.

The lesion starts as a nodule on one side (it may be bilateral) and is generally painless, or nearly so, for a period of 2–3 weeks. It can ulcerate, producing either a flat or a raised ulcer with sharp margins, a necrotic yellow slough on the base and in some cases a reddish halo. The ulcer is generally painful and tender, and when left undisturbed (or following a simple biopsy) slowly but spontaneously heals in 6–8 weeks. No recurrence has been noted in any of the reported cases and in one patient who had incomplete excision (with disease in the excised margin) no recurrence was seen at 8 years (Abrams et al., 1973).

References

ABRAMS A. M., MELROSE R. J. and HOWELL F. V. (1973) Necrotizing sialometaplasia. *Cancer* **32**, 130–135.,

BANNAYAN G., FOX G. and TILSON H. B. (1976) Necrotizing sialometaplasia of the palate. *J. Oral Surg.* **34**, 727–730.

BATSAKIS J. G. (1976) Sialometaplasia (Letter to the Editor). *Arch. Otolaryngol.* **102**, 191.

BHARGAVA S. and MONGA J. N. (1975) Necrotizing sialometaplasia of the parotid. *Indian J. Cancer* **12**, 99–101.

CRAWFORD J. M., TAUBMAN M. A. and SMITH D. J. (1975) Minor salivary glands as a major source of secretory IgA in the human oral cavity. *Science* **190**, 1206–1209.

FECHNER R. E. (1977) Necrotizing sialometaplasia. *Am. J. Clin. Pathol.* **67**, 315–317.

JOHNSON W. H. (1977) Necrotizing sialometaplasia involving the mucous glands of the nasal cavity. *Hum. Pathol.* **8**, 589–592.

MAISEL R. H., JOHNSTON W. H., ANDERSON H. A. et al. (1976) Necrotizing sialometaplasia involving the nasal cavity. *Laryngoscope* **86**, 429–434.

MYERS E. N., BANKACI M. and BARNES E. L. jun. (1975) Necrotizing sialometaplasia. *Arch. Otolaryngol.* **101**, 628–629.

PHILIPSEN H. P., PETERSEN J. K. and SIMONSEN B. H. (1976) Necrotizing sialometaplasia of palate. *Int. J. Oral Surg.* **5**, 292–299.

PINDBORG J. J. and HARDER F. (1977) Palatinal nekrotiserende sialometaplasia. *Ugeskr. Laegr.* **139**, 657–659.

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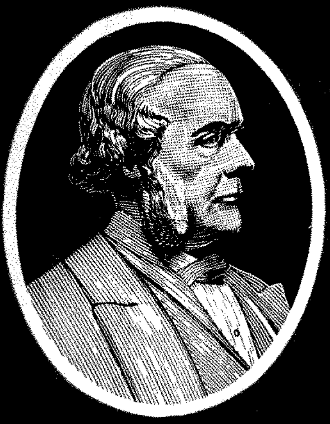

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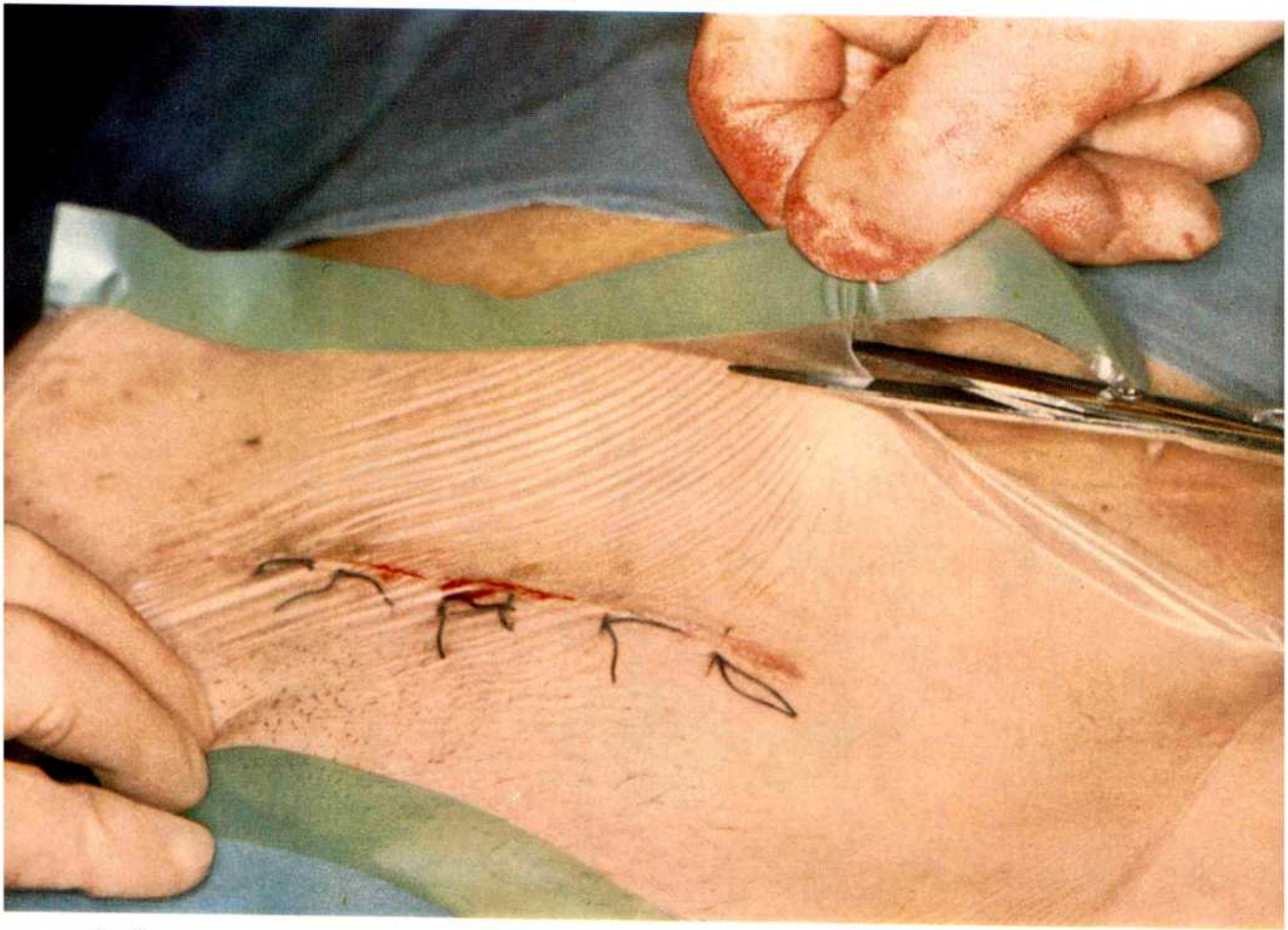

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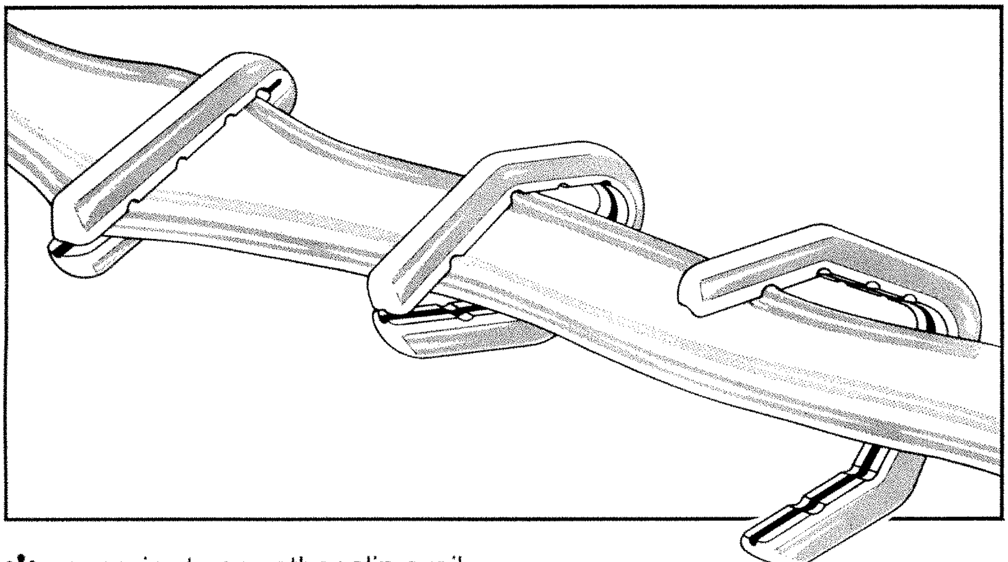

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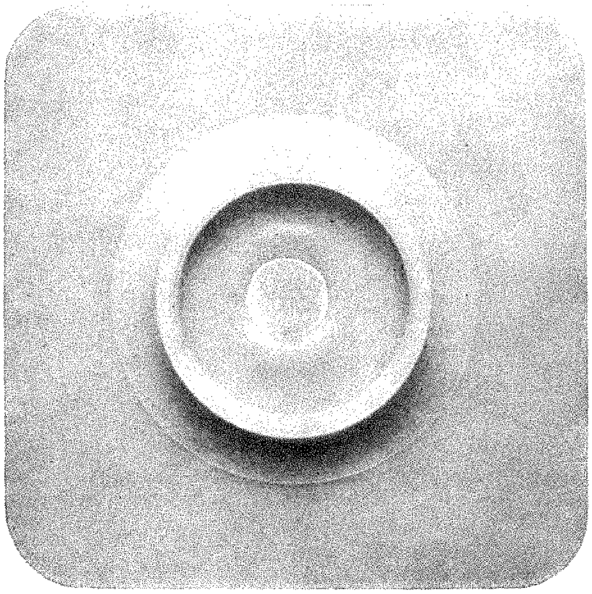

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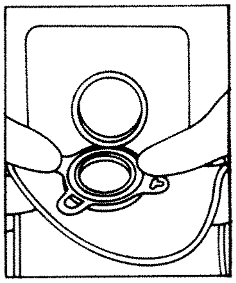

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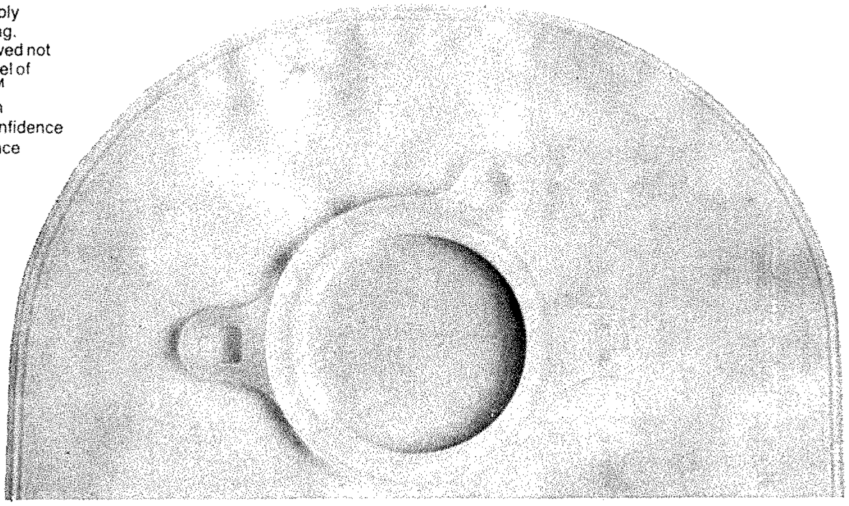

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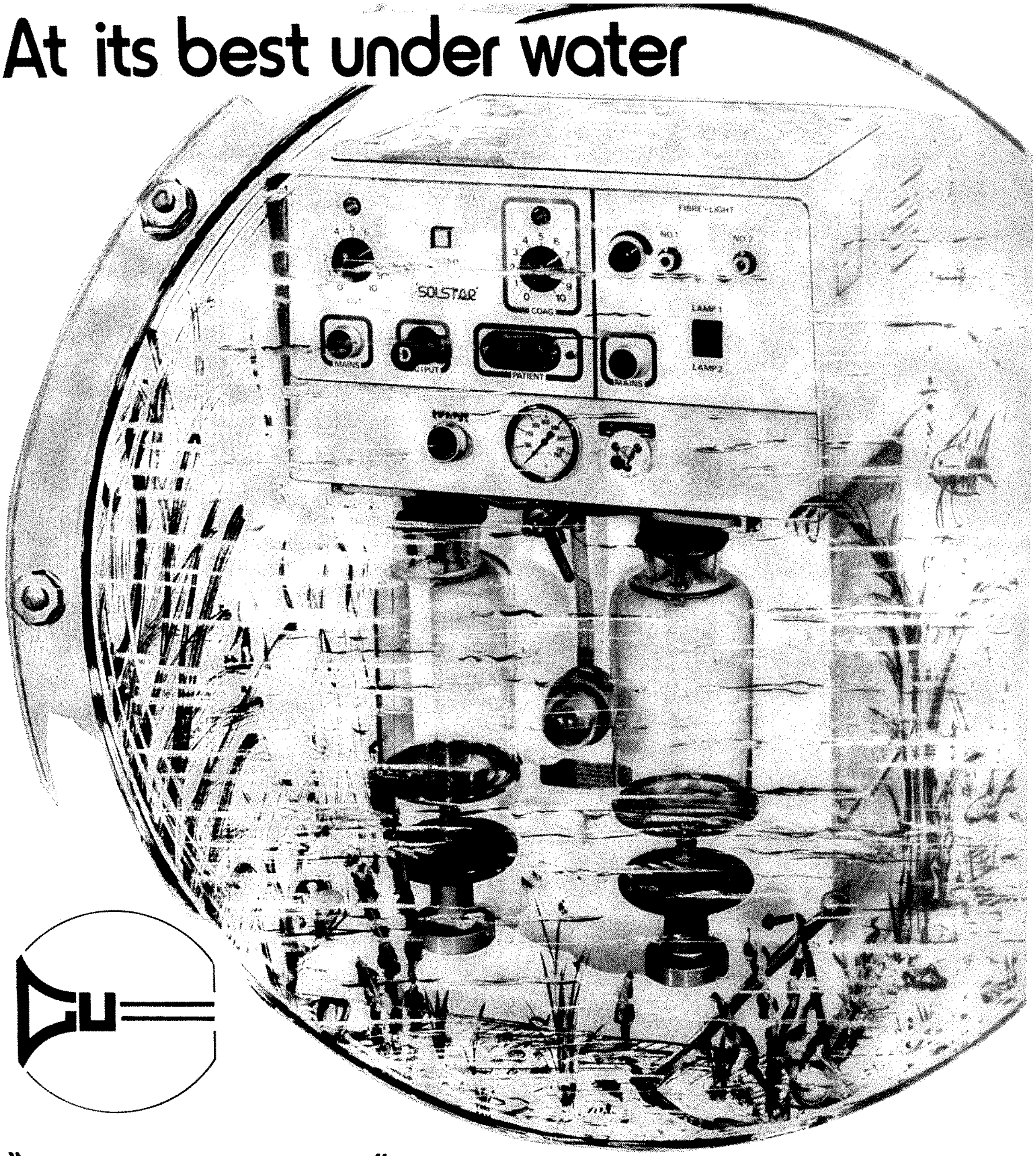

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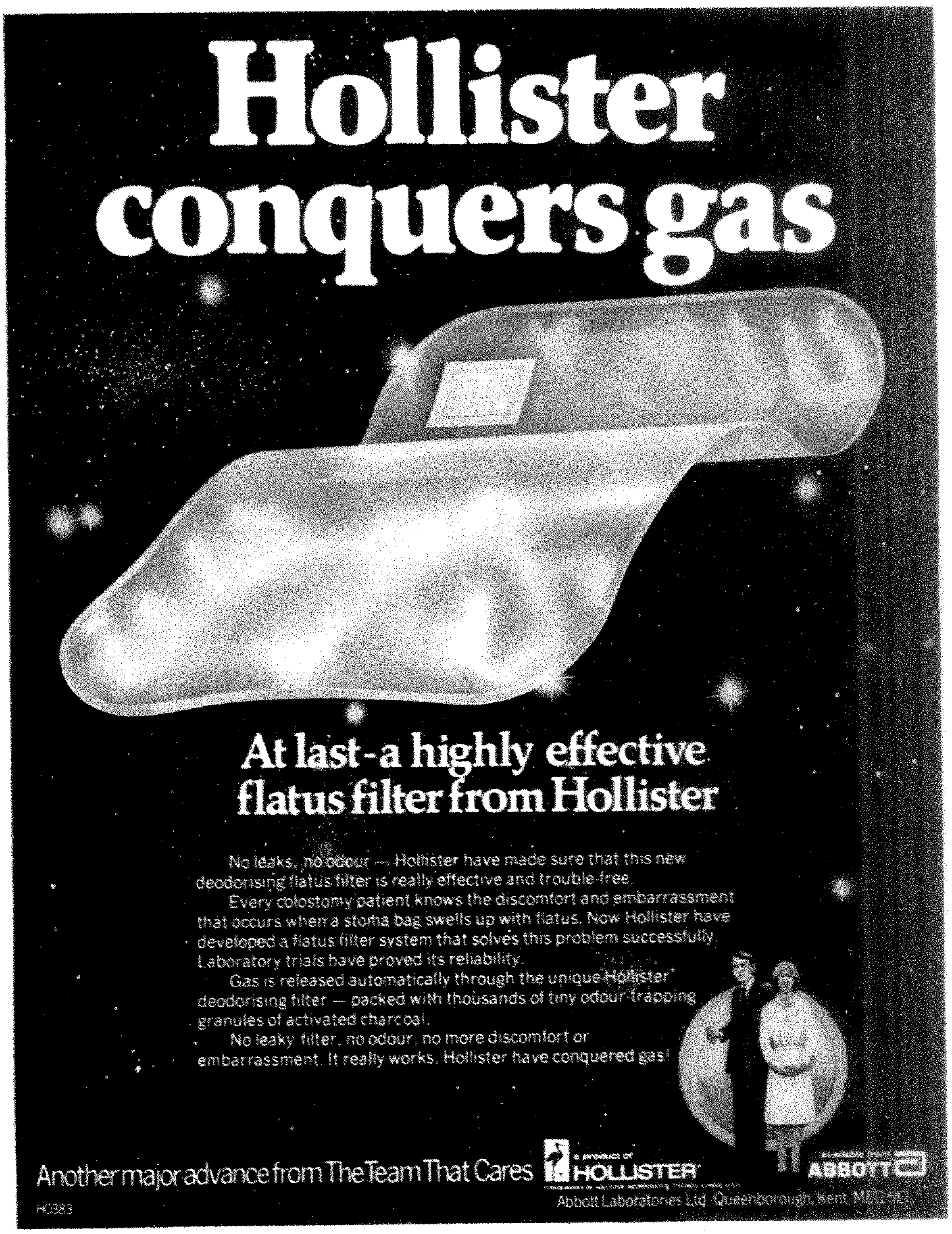

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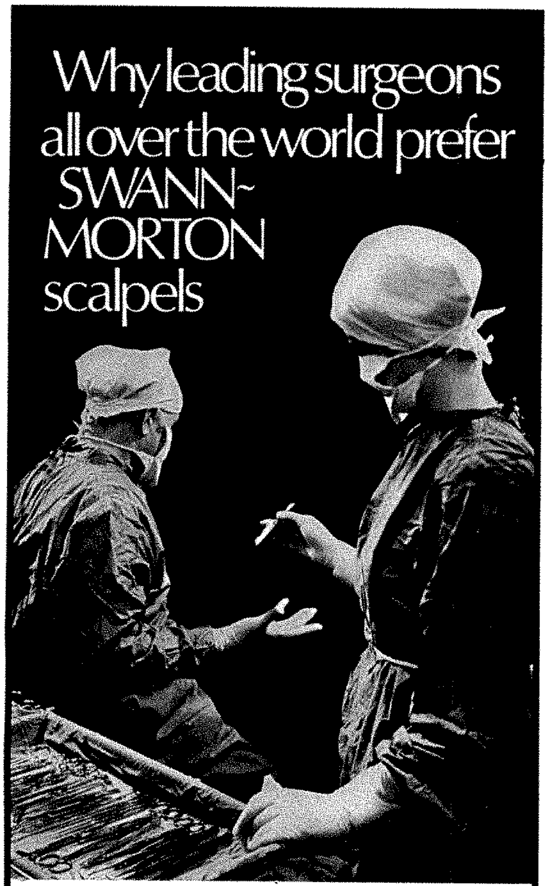
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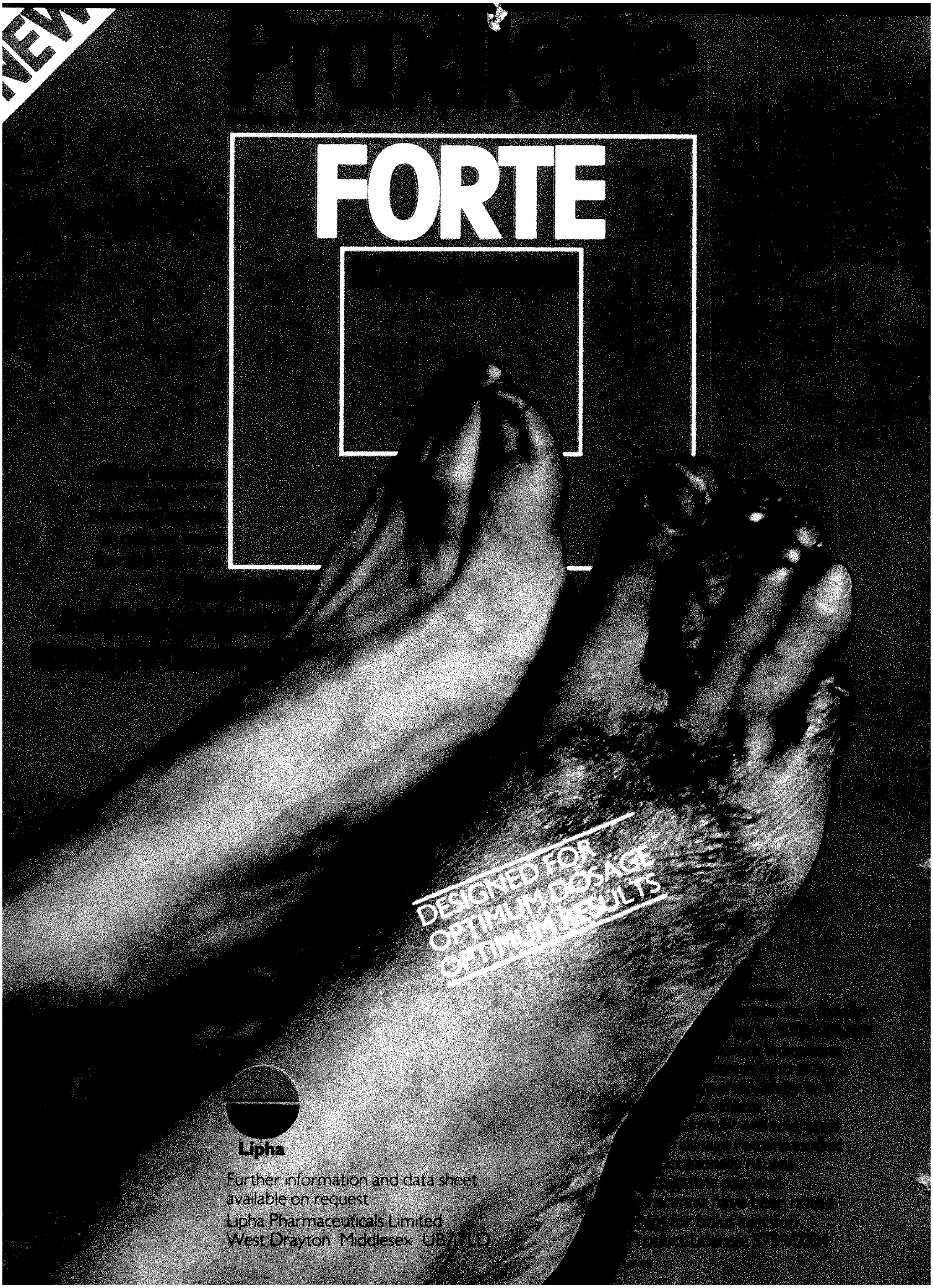

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Immunity in malignant disease*

MICHAEL WOODRUFF†

WHAT is meant by *tumour immunology*? A possible definition of an immunological reaction is a response triggered by antigen and mediated by specific antibody or specifically sensitized lymphocytes. In the present context this is too restrictive and I propose to regard tumour immunology as embracing all those aspects of the host reaction that depend on recognized differences between tumour cells and normal cells. The discussion will therefore embrace aspects of tumour biology that a purist might prefer to call para-immunological.

Let us begin, however, not with immunology but with some dogmas concerning cancer which were current when I was a medical student, and have been a long time a-dying. Here they are: the cause of cancer is largely unknown; cancer is often of multifocal origin; lymph nodes provide an efficient, albeit temporary, barrier to the spread of cancer via lymphatics; dissemination of cancer via the bloodstream occurs only late in the life-history of a tumour; cancer is autonomous.

Aetiology of cancer

It is generally accepted that the primary event in the development of a tumour is a heritable change—either a mutation or series of mutations, or a so-called epigenetic change of the kind which underlies the process of differentiation during embryological development—in one or more cells, as a result of which the response of the cell and its descendants to factors that regulate the growth of normal cells is profoundly altered. How are such changes, genetic or epigenetic, brought about?

It is commonplace to describe human tumours as spontaneous, in contrast to tumours in experimental animals which are often induced with chemical carcinogens, or by radiation, viruses or other agents. This can, however, be dangerously misleading. If by spontaneous we mean that human tumours are not deliberately induced we may be open to criticism on semantic grounds but what we are saying is, in the main, true. If we mean that, for a given tumour, no aetiological agent has yet been identified, what we are saying may be true today but false tomorrow. If we mean that human tumours, as a general rule, develop independently of any external agency—*sua sponte*—we are in terms of meaning beyond reproach but what we are saying is false, for if one looks at the whole spectrum of human cancer it seems clear that, as with animal tumours, environmental and genetic factors may both be concerned in a cause.

I would like to discuss briefly the evidence in respect of chemical carcinogens, radiation and oncogenic viruses, because tumours induced with these agents in animals have important immunological properties which can be exploited therapeutically. Human tumours similarly caused might be reasonably expected to have similar properties.

It is over 200 years since Percival Pott suggested that the high incidence of carcinoma of the scrotum in chimney sweeps in England was due to prolonged contact with soot, though it was not until 140 years later that it was shown that skin cancer could be induced in experimental animals with coal tar. In 1930 Kennaway and Hieger succeeded in inducing cancer experimentally with a pure chemical substance, 1,2,5,6-dibenzanthracene, and since then well over a hundred compounds have been shown to be carcinogenic in experimental animals. It may be added, in parentheses, that with many of these so-called carcinogens it is their metabolic products rather than the parent substances which are carcinogenic, but this does not invalidate the argument.

When I was a student we had all, even in far-off Australia, heard of Pott's chimney sweeps, and of the aniline dye workers in Germany who frequently developed bladder cancer, but we thought of these as geographical curiosities that had little in common with the tumours we were likely to encounter. Today this view is no longer tenable in the light of the high correlation between the incidence of familiar tumours and exposure to substances known to be carcinogenic in animals, of which the best known example is, of course, the association between smoking and lung cancer. The conviction is growing that, as Sir Richard Doll and others have maintained, carcinogenic chemicals play a major role in the cause of human cancer.

Ionizing radiation is a powerful mutagen and can cause visible structural damage to chromosomes. It is also carcinogenic, as has been tragically demonstrated in many fields: the high incidence of various forms of cancer in the pioneers of radiology; in people employed in painting watch dials with luminous paint when this contained radium or mesothorium; in patients given Thorotrast for radiological visualization of the liver, or, more recently, X-ray therapy for ankylosing spondylitis; in children irradiated *in utero* in the course of radiological investigations on their mothers, or subsequently for haemangiomas or other conditions; and in patients exposed to radiation as the result of the atomic bombs dropped on Hiroshima and Nagasaki.

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Ultraviolet radiation, though non-ionizing, is also both mutagenic and carcinogenic and epidemiological studies have established a strong relationship between exposure to solar ultraviolet radiation and the incidence of cutaneous basal cell carcinoma, squamous cell carcinoma and malignant melanoma.

The role of viruses in human cancer is unclear. Direct evidence that a particular kind of human cancer is caused by a virus could only be obtained by totally unethical experimentation or as the result of an unfortunate accident in which people were injected with a vaccine which contained an active oncogenic virus. The case must therefore rest on circumstantial evidence. It would lead us too far afield to discuss this. Suffice it to say that there are strong grounds for believing that a DNA virus of the herpes group, the Epstein–Barr virus (*see* Epstein, 1970), plays an essential role in the cause of Burkitt's lymphomas and of squamous cell carcinoma of the nasopharynx as seen in Asia and parts of Africa; and some grounds for suspecting that the same virus may be concerned in carcinoma of the cervix. It also seems possible that an RNA virus, rather like the mouse mammary tumour virus, may play a part in breast cancer and other similar viruses may be implicated in osteogenic sarcoma and some forms of leukaemia.

Multifocal or monoclonal origin

As a medical student I had the great privilege of being introduced to the pathology of tumours by Dr Rupert Willis. He maintained, and other pathologists with a wide knowledge of human cancer and of precancerous lesions have continued to maintain, that many tumours are of multifocal origin. In recent years, however, it has become increasingly apparent that many tumours are to a large extent monoclonal, i.e. that the tumour cells are the descendants of a single somatic cell. The evidence for this is the discovery of a high degree of uniformity in respect of marker chromosomes and tumour-associated antigens; that plasma cell tumours, including human myelomas, produce one single immunoglobulin; and that heterogeneity which occurs in the normal tissues in women as the result of random inactivation of one X chromosome is often not found in tumours.

The last of these criteria has been widely used. The marker generally employed is the enzyme glucose-6-phosphate dehydrogenase (G-6-PD), which is the product of a gene carried on the X chromosome and exists in two forms, A and B, which can be easily distinguished by electrophoresis. Women who are heterozygous at the G-6-PD locus have two populations of normal cells, one producing the A form of the enzyme and the other the B form. However, if a tumour in such an individual is monoclonal, all the tumour cells should produce the same form of the enzyme, A or B, depending on which population the cell that gave rise to the tumour belonged to. This has proved to be the case with various neoplasms studied by Fialkow and others, including uterine fibroids, Burkitt's lymphoma, chronic myeloid leukaemia and carcinoma of the cervix, though not with others, including, for example, neurofibromas (Friedman and Fialkow, 1976). While some of the evidence is open to criticism on the grounds of the small numbers of tumours studied, it is, in general, highly convincing.

Can one reconcile a multifocal origin with evidence of monoclonality? It seems to me that one can, because a tumour which appears at a particular time to be monoclonal was not necessarily so *ab initio*; it may have become monoclonal because one particular clone of cells outgrew all others. Even when one clone predominates, the presence of a small number of foreign cells cannot be ruled out. As we shall see, many tumours contain dormant cells and there is no obvious reason why these should all belong to the dominant clone; indeed, the recent discovery by Pimm and Baldwin (1977) with experimental tumours, that cells from local recurrences following incomplete surgical excision differ antigenically from the original tumours, raises the possibility that dormant cells which are not members of the dominant clone may be responsible in some patients for local recurrence and perhaps also for the appearance of metastases, after surgical excision or radiotherapy.

When does dissemination occur?

Since 1863 when Virchow postulated that lymph nodes filter out particulate matter from lymph, it seems to have been widely accepted that they constitute an effective, albeit temporary, barrier to the passage of tumour cells. Experiments in animals have now shown two things. First, that radioactivity-labelled, but viable, tumour cells can pass through lymph nodes in a matter of minutes although dead cells may be trapped for a long time (Fisher and Fisher, 1966). Secondly, that the nodes draining tumour transplants, which rarely cause lymph node metastases, contain a number of tumour cells that are difficult to account for except on the basis that they are in process of traversing the node and will eventually reach the bloodstream (Hewitt and Blake, 1975).

Blood-borne dissemination has traditionally been regarded as a relatively late occurrence with many tumours. This belief provides the rationale for forms of treatment which are directed only to the local tumour and related lymph nodes. The demonstration at the time of operation of tumour cells in the bloodstream shows that dissemination may occur at least as early as this, and it is clear from the incidence of metastatic disease after adequate local excision of early primary tumours that tumour cells disseminated before or during operation quite often give rise to clinical metastases. That cells disseminated well in advance of operation can do this is clear from the work of Galasko (1975) and others on bone scanning in patients with breast cancer.

Attempts have been made to determine the time at which metastatic deposits in the lungs begin by observing the growth rate of each deposit from the time when it is first clearly recognizable in serial chest X-rays and extrapolating the growth curve back to the time when the estimated size of the metastasis was about that of a single cell. It is now clear that if a simple logarithmic growth curve is fitted the estimated time of origin may be far too early, but if a rather more complex method which allows for a decline in growth rate with increasing age (a Gompertz curve) is used, the estimate is likely to be much nearer to the truth. Such evidence as there is confirms that dissemination leading to metastasis can occur much earlier than we used to believe and quite often before patients present for treatment, even when there has been no undue clinical delay. It is this early dissemination which so often makes treatment in the form of surgical excision of a primary tumour, even with its possible lymph node metastases, insufficient and, if I may anticipate my later argument, I would add that our successes are probably often due not to our having removed *every* cancer cell, but to our having reduced the residual tumour burden to a level at which it can be dealt with by other mechanisms.

Autonomy

Not so long ago it was widely accepted that malignant tumours are, as Ewing (1940) expressed it, autonomous new growth of tissue. This dogma seems to have implied, first, that tumours are not influenced by any of the factors that control the growth and equilibrium of normal tissues, and, second, that no special homeostatic mechanisms, even of a rudimentary kind, exist for controlling carcinogenesis and tumour growth.

The falsity of the first of these dogmas became apparent when the fact that some tumours are hormone-dependent was firmly established by Huggins (1967). The case against the second may be considered under four headings: evolutionary considerations, clinical observations, studies of tumour cell population kinetics and immunological evidence.

It seems unlikely on evolutionary grounds that complex multicellular organisms could have developed as they have had they not evolved mechanisms to deal with what have been called asocial cells, i.e. cells which have survival advantages as cells but which are disadvantageous from the point of view of the organism as a whole. Cancer cells clearly fall in this category. The relevant clinical observations in this context are the occasional spontaneous regression of primary tumours, and of metastases after excision of a primary tumour, and the appearance and rapid growth of metastases after a long latent interval. Regression has been carefully investigated by Everson and Cole (1966). In summary, in a review of the literature covering the period 1900–66, they found 64 cases of regression of a primary tumour (including 19 neuroblastomas, 10 carcinomas of the bladder, 9 soft tissue sarcomas, 5 carcinomas of the colon or rectum and 4 carcinomas of the stomach) following either biopsy or manifestly incomplete excision, or, in the case of the bladder tumours, urinary diversion. They also collected 106 cases in which metastases had regressed, usually after excision of the primary tumour; these included 23 patients with carcinoma of the kidney, 19 with neuroblastoma and 15 with malignant melanoma. In patients with multiple subcutaneous melanomatous deposits, Bodenham (1968) made the extremely interesting observation that even though the total number of nodules was increasing, some could be observed to disappear. It is worth noting that this observation, which seems to me to be of great biological importance, was made with nothing more complicated than an ordinary camera and some black and white film.

The sudden appearance and rapid growth of local recurrence and metastases after a long latent interval have also been documented by Everson and Cole (1966), who collected almost 100 cases in which this occurred 10–50 years after removal of the primary tumour. However, instead of referring to their cases I would like to mention two from my own experience, although the latent interval was not quite so long.

The first was a patient who presented with an operable (stage II) carcinoma of the breast and a history of having had a melanoma removed from the foot 3 years previously. She was treated by radical mastectomy and postoperative X-ray therapy. There had been no evidence of local recurrence of the melanoma, or of metastasis, before this treatment, but 6 weeks after operation melanomatous nodules appeared, first in the field of irradiation and then elsewhere, and about 4 months later the patient was dead with metastatic melanoma in the lungs, liver, bone-marrow and brain. It seems clear that in this case the trauma of the operation or the radiotherapy, or both together, brought about some change in the tumour–host relationship, and there is no knowing how long the residual melanoma cells that gave rise to the metastases might have remained dormant had this not occurred.

Often, however, no cause for the sudden appearance of metastases can be discerned. This is illustrated by my second example, a patient who presented with a huge clear cell carcinoma of the right kidney and a history that the left kidney had been removed for a carcinoma 4 years previously. He was treated by transplantation of a kidney from a cadaver, followed by right nephrectomy, in the course of which it was found that the renal vein was invaded by tumour. Despite this, and the fact that he received routine immunosuppressive treatment, the patient remained well for 7 years, without evidence of local recurrence or metastasis. He then began to lose weight and a radiograph of the chest raised a suspicion of pulmonary metastases. Within a few months he was dead with numerous metastases in the lungs and liver.

Tumour cell population kinetics

A tumour is not simply a mass of neoplastic cells but a complex eco-system, which includes neoplastic cells —both living and dead—non-neoplastic cells such as lymphocytes, polymorphs and macrophages and a supporting stroma of vascular connective tissue. Studies of tumour cell population kinetics, based on measurements of the proportion of cells in mitosis after administration of so-called stathmokinetic agents like colchicine and vincristine which cause dividing cells to be arrested in metaphase, and measurement of the proportion of labelled mitoses in autoradiographs of biopsy specimens obtained after injecting tritiated thymidine or of small fragments of tumour tissue treated with this material *in vitro*, have established, first, that with both animal and human tumours only a proportion of the neoplastic cells are proliferating at any given time, and secondly, that many cells are lost either by emigration from the tumour or by cell death. Some of the non-proliferating cells are end-state cells which will die without dividing again; others, referred to variously as dormant or G_0 cells, may resume cycling.

Immunological evidence

Many animal and human tumours possess tumour-associated surface antigens (TAA) which are not present on the surface of normal cells. A subset of these antigens, termed tumour-associated transplantation antigens (TATA), evoke a reaction damaging to the tumour when it is transplanted to a recipient of the same genetic constitution as the autochthonous host (i.e. the individual in which the tumour originated) and some or all of these may evoke a reaction damaging to the tumour in the autochthonous host itself. TAA have been demonstrated by a variety of immunological techniques in many animal and human tumours; so-called carcinoembryonic antigen provides an example of human TAA. The presence or absence of TATA in animal tumours is determined by transplanting the tumour to another animal of the same inbred strain or to an identical twin. The first of the procedures is clearly not available in man and, although the second has been used occasionally, it may be dangerous and is unjustifiable. In animals, however, TATA occur characteristically with tumours induced with chemical carcinogens or viruses and it would be surprising if human tumours of similar origin did not also express antigens of this kind.

The discovery of TATA is the basis of the hypothesis of immunological surveillance of Thomas and Burnet (*see* Burnet, 1970), according to which the incidence and growth of malignant tumours are limited by homeostatic mechanisms of an immunological kind. It is apparent that such mechanisms, if they exist, are far from perfect, otherwise no one would ever get a tumour. Various mechanisms by which a tumour may escape destruction have been postulated. By contrast, some people believe, and it is impossible to disprove, that homeostatic mechanisms of some kind are responsible for the fact that we do not all die of cancer at an early age.

In recent years Burnet's hypothesis has been criticized on the ground that, if it were true, the incidence of spontaneous tumours in congenitally athymic mice, and in patients who are congenitally immunodeficient or have been treated for a long time with immunosuppressive drugs, should be much higher than it is. This criticism tells more strongly against the notion that the T lymphocyte plays a key role in surveillance than against the concept of surveillance itself, and there is a growing body of experimental evidence that macrophages and the as yet not completely identified natural killer (NK) cell may play an important role in surveillance. If surveillance does occur then this has important therapeutic implications. On the one hand, the possibility exists that some forms of treatment may weaken resistance to a tumour; on the other hand, there is the encouraging possibility that it may be possible to exploit and augment natural defence mechanisms by therapeutic means.

The suggestion that it might be disadvantageous to extirpate the axillary lymph nodes in patients with breast cancer was first made by a radiotherapist, Robert McWhirter (1955), though for a reason not directly concerned with my present argument. Today, however, a growing number of surgeons like George Crile and Michael Baum are questioning the wisdom of *routinely* ablating lymph nodes in relation to a tumour by either block dissection or radiotherapy, and the possible harmful effects of chemotherapy on the lymphoreticular tissues is very much in the minds of many people, including, I am glad to say, quite a number of those who use this form of treatment.

The possibility of augmenting natural homeostatic mechanisms by immunological and para-immunological means is being extensively studied in experimental animals and many clinical trials have begun. The procedures used are of two kinds: specific procedures designed to augment the patient's reaction to the TATA of his particular tumour and non-specific procedures which might be expected to increase his capacity to respond to tumours in general. Here, I will mention only one approach, chosen neither at random nor because I can say with confidence that it is the most promising, but because it is the one with which I am most familiar. I refer to non-specific immunopotentiation (in the broad sense of the term) with one particular agent, namely, a killed vaccine of *Corynebacterium parvum.* James Boak and I first demonstrated the anti-tumour effect of this material experimentally (Woodruff and Boak, 1966) when we showed that it would delay the appearance of an isogenically transplanted tumour and it has been confirmed that it potentiates the effect of chemotherapy in dealing with established tumour transplants. The material is normally given intravenously or (in animals) intraperitoneally; it is also highly effective with some tumours when injected locally, but for this effect T lymphocytes are required whereas when given systemically this is not the case. A recent finding is that the effect of chemotherapy may be potentiated by *C. parvum* even in the case of a tumour of spontaneous origin which appears to be virtually non-immunogenic (Woodruff et al., 1978).

It seemed likely, and the available evidence supported this view, that if immunotherapy was going to achieve anything, it would be most effective when the patient's tumour burden had been drastically reduced by surgical excision of the primary tumour, by radiotherapy or by chemotherapy. After an initial study in patients with advanced cancer, therefore, a randomized trial of *C. parvum* as an additional treatment following pulmonary resection for operable lung cancer was set up in Edinburgh. All the patients admitted to this trial had had either a lobectomy or a pneumonectomy for histologically proved bronchogenic cancer and a random sample of the patients received in addition a single intravenous infusion of *C. parvum.* This produces a febrile reaction, which may be quite severe but, if certain precautions are observed, has proved in the experience of ourselves and others to be otherwise well tolerated. While it is too early to draw firm conclusions, since many of the patients with squamous cell lesions in both the *C. parvum* treated and the control groups are still alive, I doubt whether the additional treatment has made very much difference, but it has certainly not proved disadvantageous. The next step, clearly, is to study the effect of repeated treatment with *C. parvum,* since in animal experiments this can be more effective than a single dose. A second trial has therefore been set up, in which thoracic surgeons in a number of centres have agreed to participate.

I see no good reason to advise you at the present time to make radical changes in the way in which you manage patients with cancer, though I am inclined to suggest a fairly conservative attitude towards lymph nodes which are not obviously involved with tumour.

There may well be important changes needed in our management of malignant disease, but it is my guess that excision of primary tumours will continue for a long time to play an important role in the treatment of cancer; it is, however, not a guess but a certainty that this alone in many patients is not enough. Additional forms of treatment are needed to deal with residual disease, even when, indeed especially when, the residual disease is still occult, for that is when treatment is most likely to be successful. The

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1. *Cancer Treatment Reports* (1976), **60**, 1431.
2. *British Journal of Cancer* (1971), **25**, 270

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1) Schneider et al., Chirurg **47,** 185 (1976)
2) McMichan et al., Med. Welt **27,** 2331 (1976)

development of such new procedures requires both laboratory research and clinical trial; clinical trials are only possible if practising clinicians are prepared to participate. Of course I am not asking you to participate in any trial which you regard as unjustifiable from the point of view of your patients; on the other hand, I urge you not to refuse to participate in a trial simply because it is going to involve some hard work.

References

BODENHAM D. C. (1968) A study of 650 observed malignant melanomas in the South-west region. *Ann. R. Coll. Surg. Engl.* 43, 218–239.

BURNET F. M. (1970) *Immunological Surveillance.* Sydney, Pergamon Press.

EPSTEIN M. A. (1970) Aspects of the EB virus. *Adv. Cancer Res.* 13, 383–411.

EVERSON T. C. and COLE W. H. (1966) *Spontaneous Regression of Cancer.* Philadelphia, Saunders.

EWING J. (1940) *Neoplastic Diseases: a Treatise on Tumors,* 4th ed. Philadelphia, Saunders.

FISHER B. and FISHER E. R. (1966) The interrelationship of hemotogenous and lymphatic tumor cell dissemination. *Surg. Gynecol. Obstet.* 122, 791–798.

FRIEDMAN J. M. and FIALKOW P. J. (1976) Cell marker studies of human tumorigenesis. *Transplant Rev.* 28, 17–33.

GALASKO C. S. B. (1975) The significance of occult skeletal metastases, detected by skeletal scintigraphy, in patients with otherwise apparently 'early' mammary carcinoma. *Br. J. Surg.* 62, 694–696.

HEWITT H. B. and BLAKE E. (1975) Quantitative studies of translymphnodal passage of tumour cells naturally disseminated from a non-immunogenic murine squamous carcinoma. *Br. J. Cancer* 31, 25–35.

HUGGINS C. (1967) Endocrine-induced regression of cancers. *Science* 156, 1050–1054.

MCWHIRTER R. (1955) Simple mastectomy and radiotherapy in the treatment of breast cancer. *Br. J. Radiol.* 28, 128–139.

KENNAWAY E. L. and HIEGER I. (1930) Carcinogenic substances and their fluorescence spectra. *Br. Med. J.* 1, 1044–1046.

PIMM M. V. and BALDWIN R. W. (1977) Antigenic differences between primary methylcholanthrene-induced rat sarcomas and post-surgical recurrences. *Int. J. Cancer* 20, 923–932.

VIRCHOW R. (1863) Ueber bewegliche thierische Zellen. *Virchows Arch.* 28, 237.

WOODRUFF M. F. A. and BOAK J. (1966) Inhibitory effect of injection of *C. parvum* on the growth of tumour transplants in isogeneic hosts. *Br. J. Cancer* 20, 345–355.

WOODRUFF M. F. A., WHITEHEAD V. L. and SPEEDY G. (1978) Studies with spontaneous mouse tumour. I. Growth in normal mice and response to *Corynebacterium parvum*. *Br. J. Cancer.* 37, 345–355.

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Manuscripts and reference style for the *British Journal of Surgery*

Not all papers submitted to our journal or others are accepted. Submission elsewhere may then mean tedious restyling and redrafting. In order to facilitate this inevitable passage of manuscripts from one journal to another, the *British Journal of Surgery* joins with a group of like-thinking journals (1, 2, 3, 4) in asking for its manuscripts to be submitted in uniform style. Details of this, which include the method by which references should be handled in the text, will be incorporated into our Editorial Notices from the June issue. The new reference style is used in this announcement.

The *British Journal of Surgery* will follow the reference style in the list of references of the United States National Library of Medicine, which is also used in *Index Medicus*. Some details are given in our Editorial Notices but authors are advised (as they are in these notices) to refer to *British Medical Journal* 1979; 1: 532–5 or *Lancet* 1979; 1: 428–31 and to obtain copies of the Vancouver Declaration (available from the Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, at a cost of 50 p including postage).

The new style will come into use in January 1980 for Volume 67 of the *British Journal of Surgery*. Authors are requested to change their form of submission *now* to that of the new style.

References

1 INTERNATIONAL STEERING COMMITTEE OF MEDICAL EDITORS: Uniform requirements for manuscripts submitted to biomedical journals. *Br. Med. J.* 1978; 1: 1334–6.

2 LEADING ARTICLE: Declaration of Vancouver. *Br. Med. J.* 1978; 1: 1302–3.

3 EDITORIAL: Towards a common style. *Lancet* 1978; 2: 1242.

4 INTERNATIONAL STEERING COMMITTEE OF MEDICAL EDITORS: Uniform requirements for manuscripts submitted to biomedical journals. *Br. Med. J.* 1979; 1: 532–5.

Br. J. Surg. Vol. 66 (1979) 302–305

Wound drainage following radical mastectomy: the effect of restriction of shoulder movement

T. J. FLEW*

SUMMARY

A randomized prospective clinical trial has been performed to determine the effect of temporary immobilization of the shoulder on wound drainage following radical mastectomy. In 64 patients admitted to the trial the mean volume of drainage was reduced by 40 per cent in those who had shoulder movement restricted for the first 7 days after operation when compared with the group in whom early arm exercises were encouraged. The mean drainage time was reduced by 29 per cent. Shoulder immobilization did not result in increased shoulder stiffness, although there was an increased incidence of mild lymphoedema of the arm.

SUBCUTANEOUS fluid collections may complicate any operation in which large skin flaps are raised. They are frequently encountered in the postoperative care of mastectomy patients, especially after the radical operation.

The traditional practice used to be to allow the fluid to escape via one or more open drains into a thick layer of dressings held in place by careful strapping or bandaging. Compression was used to inhibit the further formation of fluid and attempts were sometimes made to obliterate the dead space and to hold the flaps still by means of sutures. Orr (1951) used tension sutures tied over rubber tubing to hold the flaps against the chest wall, Keyes et al. (1953) tried multiple silk sutures together with drains, while Larsen and Hugan (1955) stitched down the flaps with up to fifty subcutaneous cotton sutures and advised extensive early shoulder movement. These methods were not without complication and were abandoned with the introduction of continuous closed suction drainage. Here, suction is usually maintained for several days until the drainage has almost ceased and the potential dead space is obliterated by adherence of the skin flaps to the deeper structures. Murphey (1947) was the first to describe suction drainage after radical mastectomy, and its superiority over open drainage was shown by Morris (1973) and by Bourke et al. (1976). In particular, the frequency of dressings and length of time until the removal of drains are reduced, and in Morris's series there was reduction in delayed wound healing and in the length of stay in hospital.

Large skin flaps would be expected to become more rapidly adherent to the underlying structures if they were held relatively immobile rather than subject to repeated movement, with consequent reduction in fluid formation. Nevertheless, there is no conclusive evidence that this is so. Riddell (1948) advocated discouragement of all movements at the shoulder joint following radical mastectomy because 'too early movement has caused separation of the skin edges of the flaps and increased the liability to serum collection, without any compensating advantage in the ultimate range of movement at the shoulder joint'. The majority of surgeons, however, probably recommend early arm movements because of the potential risk of developing shoulder stiffness. This procedure was standard in this unit, but considerable problems arose because of persistent wound drainage continuing sometimes two or more weeks after operation.

This controlled clinical trial was carried out to determine the effect of temporary restriction of shoulder movement on the volume and duration of wound drainage following radical mastectomy. An assessment was also made of the effect of this regimen on the incidence of shoulder stiffness and lymphoedema of the arm.

Patients and methods

During 8 months in 1973, 64 consecutive patients undergoing radical mastectomy for early breast cancer were admitted to the trial. All patients were nursed in the same ward of the Guy's Breast Unit at New Cross Hospital. The operations were all modified Halsted radical mastectomies performed to a standard technique by six surgeons. Diagnosis was confirmed histologically by open biopsy, either as a separate procedure or by frozen section as a preliminary to mastectomy. Elliptical skin incisions were marked out in ink and the skin flaps infiltrated subcutaneously with a solution of 1 : 400 000 adrenaline in saline to reduce haemorrhage. The flaps were cut to include some subcutaneous fat, and mastectomy performed with complete axillary node clearance together with *en bloc* removal of pectoralis minor, and a proportion of the sternal head of pectoralis major depending on the site of the tumour. Haemostasis was achieved by diathermy, with occasional catgut ligatures. The wound was then irrigated with hot (48 °C) sterile distilled water, with the objective of lysing any seeded malignant cells. Three Redivac drains were introduced with a trocar through the lower flap, one passing beneath each flap and one into the axilla, and sutured loosely in place to the chest wall with 2/0 catgut. The wound was sutured with interrupted silk by the method of 'halving' to match the flaps equally, sprayed with Nobecutane and covered with a light gauze and wool dressing held in place with Netelast. Skin grafting was not performed. The three drainage tubes were connected to vacuumed bottles, and after release of the clamps the flaps were gently massaged to evacuate any blood which had collected before the patient left the operating table.

At this stage the patient was randomly allocated to the trial by drawing an envelope from a box. On return to the ward, those patients who drew the 'fixed' option had the shoulder on the side of operation held relatively immobile by a triangular bandage. The bandage enclosed the upper arm and was tied around the waist. This prevented abduction at the shoulder whilst allowing a certain amount of internal and external rotation but, by leaving the forearm free, did not greatly inconvenience the patient. For those who drew the 'free' option the arm was left unrestricted, and arm movements commenced under the guidance of a physiotherapist from the second postoperative day. On the seventh day the triangular bandage was removed from the patients in the 'fixed' group and the same programme of arm movements was begun under supervision.

In both groups the wool was removed from beneath the Netelast on the third postoperative day, leaving a light gauze dressing covering the wound. Provided wound healing was satisfactory, one-third of the sutures were removed on the

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tenth day, one-third the next day and the remainder on the twelfth day. The drainage bottles were changed as often as necessary, and the volume of fluid in each was measured daily. Each drain was removed when it had produced 20 ml or less on 3 consecutive days. At subsequent inspection if a seroma had collected beneath the flaps it was aspirated by means of a needle and vacuumed tube (Vacutainer). This was repeated as required on an in- or outpatient basis until the reaccumulation of fluid had ceased. The total volume of drainage, the length of time until the removal of the last drain and the number and volume of aspirations were recorded.

All patients were assessed preoperatively, 2 weeks postoperatively and again as outpatients 1 month and 4 months after discharge from hospital. The wounds were inspected at least every 3 days until discharge from hospital, and if not then healed they were checked again weekly until healing was complete.

The following data were recorded:

Shoulder movements

1. Abduction and elevation (0–180°).
2. Internal and external rotation with the upper arm abducted to horizontal and the elbow flexed to 90°.

A note was also made of subjective shoulder stiffness and of any additional physiotherapy required following discharge from hospital.

Lymphoedema

The circumference of both arms was measured at points 20 cm above and 10 cm below the olecranon.

Wound healing

1. Delay in healing: (*a*) breakdown of the wound, defined as separation of the wound edge over any length; (*b*) necrosis of the flaps, judged as any area of sloughing greater than 5 mm in diameter at 14 days; (*c*) delay in removal of sutures beyond 12 days.
2. Wound infection, defined as purulent discharge from the wound, pus that could be aspirated, or cellulitis of the skin flaps associated with a pyrexia greater than 38 °C.
3. Wound haematoma, defined as a collection of fluid beneath the flaps which, when aspirated, appeared to be frank blood.

Clinically apparent postoperative chest infection and deep vein thrombosis were also recorded, as were any other significant complications.

The majority of patients received postoperative radiotherapy. Those with clinically uninvolved axillary nodes were part of another trial then in progress to compare radical mastectomy with wide excision of the lump in the treatment of 'early' breast cancer, and all received radiotherapy. Radiotherapy was only given to those with clinically malignant nodes if involvement was confirmed histologically. After the wound was fully healed, treatment was given to the axilla, supraclavicular triangle and internal mammary chain, in a dose of 3000–3300 rad given over 3 weeks. The percentage of patients who received radiotherapy was similar in the two groups (*Table I*), and all had completed treatment by the time of their follow-up examination at 4 months.

Results

Sixty-four patients were admitted to the trial. In the group with the arm unrestricted ('free') there were 29 patients whose age range was 28–77 years (mean 53·5 years). In the group with shoulder restriction ('fixed') there were 35 patients whose age range was 27–72 years (mean 51·4 years). *Table I* shows that the two groups were similar with respect to tumour size, lymph node involvement, radiotherapy and subsequent recurrence, thus excluding bias. The results were assessed statistically using Student's t test and the χ^2 test with Yates's correction.

Wound drainage (Table II)

In the 'free' group mean drainage volume was 1203·1 ml and mean total drainage time (including aspirations) 16·4 days, compared with 725·4 ml and 11·7 days respectively in the 'fixed' group of patients. These reductions in drainage volume and duration are significant ($P<0{\cdot}01$ and $P<0{\cdot}05$ respetiveely). Time postoperatively until the removal of the last drain was reduced from a mean of 13·7 days in the 'free' group to a mean of 11·2 days in the 'fixed' group, and there was a small reduction in the length of stay in hospital, but these differences are not statistically significant.

Table I: COMPARISON OF TRIAL GROUPS

	Fixed	Free
No. of patients	29	35
Age (yr)		
Mean	53·5	51·4
Range	28–77	27–72
Involved axillary nodes		
No. of patients	13 (44·8%)	15 (42·9%)
Mean no. of nodes	2·5	1·9
Postoperative radiotherapy		
No. of patients	21 (72·4%)	24 (68·6%)
Tumour recurrence at March 1978 (4½–5 yr)		
Recurrence	10 (34·5%)	12 (34·3%)
Died	6 (20·7%	8 (22·9%)

Table II: WOUND DRAINAGE

	Fixed (n = 29)		Free (n = 35)	
Drainage volume (ml, mean±s.e.)	725·4±77·3		1203·1±137·7†	
Drainage time (d)				
Total* (range and mean)	4–21	11·69±0·93	6–60	16·40±1·79‡
Until removal of all drains (range and mean)	4–21	11·17±0·92	6–31	13·66±0·93§
Aspirations				
No. of patients	2		7§	
No. of aspirations	4		33‖	
Hospital stay (d, mean±s.e.)	14·66±0·66		16·03±0·75§	

* Including aspirations.

Significance: † t = 2·862; $P<0{\cdot}01$. ‡ t = 2·195; $P<0{\cdot}05$. § n.s. ‖ t = 1·791; $P<0{\cdot}1$.

Table III: SHOULDER ABDUCTION AT 4 MONTHS

	Shoulder abduction	
Group	Limitation>30° (no. of patients)	Mean limitation (degrees±s.e.)
Fixed (n = 29)	8	19·8±3·3
Free (n = 34)	13	21·2±3·6

The differences are not significant.

One patient in each group had a pocket of fluid aspirated before removal of the last drain. Following removal of all drains, 7 patients in the 'free' group had a total of 33 aspirations up to 60 days postoperatively, compared with only 2 patients requiring a total of 4 aspirations up to 18 days postoperatively in the 'fixed' group.

Shoulder stiffness (Table III)

One patient in the 'free' group died from metastatic disease just before her 4-month assessment was due and is therefore not included in the follow-up. No patient had restricted shoulder movement before mastectomy. There was no postoperative limitation

Table IV: LYMPHOEDEMA AT 4 MONTHS

	Fixed ($n = 29$)	Free ($n = 34$)
No. of patients with lymphoedema*		
1 0–2·5 cm	15	7†
2·5–4·5 cm	3	3‡
>4·5 cm	1	0‡
Lymphoedema (cm)		
20 cm above olecranon	0·88±0·23	0·57±0·19‡
10 cm below olecranon	0·83±0·25	0·22±0·21§

* Maximum of measurements above and below the olecranon. Significance: † $\chi^2 = 5·377$; $P < 0·02$. ‡ n.s. § $t = 1·852$; $P < 0·1$.

Table V: OTHER COMPLICATIONS

	Shoulder restriction	
	Fixed ($n = 29$)	Free ($n = 35$)
Delayed discharge from hospital (beyond 12 d)	16	24
Delayed wound healing	8	12
Wound sepsis	5	4
Haematoma	1	2
Chest infection	1	1
Deep vein thrombosis	0	1*
Thrombophlebitis of arm	1	0
Late physiotherapy required	0	1

No significant differences.
* Patient died with metastases 4 months post-mastectomy.

of internal or external rotation at the shoulder in any patient at 4 months. Early in the postoperative phase there was considerable impairment in arm abduction in the 'fixed' group, but at 4 months there was no significant difference between the two groups. Only 1 patient, who had not had her arm restrained, had stiffness of the shoulder sufficient to require physiotherapy as an outpatient.

Lymphoedema (*Table IV*)

At 4 months there was mild lymphoedema (1·0–2·5 cm) in 15 patients in the 'fixed' group, compared with only 7 in the 'free' group ($P < 0·02$). There were 3 patients in each group at this time with moderate swelling (2·5–4·5 cm) and only 1 patient had severe lymphoedema (>4·5 cm). This patient, from the 'fixed' group, had only mild swelling of the upper arm, but had a 5·1-cm increase in forearm circumference. Overall, there was a mean increase in forearm circumference of 0·83 (±0·25) cm in the 'fixed' group compared with a mean increase at the same site in the 'free' group of 0·22 (±0·21) cm at 4 months ($P < 0·1$).

Other complications (*Table V*)

There was no significant difference in the rate of delayed wound healing beyond 12 days in the group that commenced arm exercise early, and no patient had suture removal delayed. The rates for other complications were similar, but the numbers were small.

Discussion

This trial has demonstrated that by limiting shoulder movement for 7 days postoperatively the amount of fluid drained from a radical mastectomy wound can be reduced by an average of 40 per cent, while the length of time until fluid formation ceases is reduced by about 29 per cent. As well as being a consequence of stabilization of the skin flaps, this is probably also due in part to a lessening of drainage from severed axillary lymphatics.

The results also suggest that an increase in the incidence of lymphoedema might be anticipated from routinely employing this method of postoperative care. The incidence of post-mastectomy lymphoedema varies in different series from 8 to 80 per cent (El-Kharadly and Enein, 1965) and is principally affected by the extent of surgery, the type and dose of radiotherapy and the incidence of infection. Atkins et al. (1972), in a series of 90 patients also treated at Guy's Breast Unit, reported an incidence of 81 per cent 3 months after radical mastectomy, 71 per cent being classed as mild (0–2·5 cm), 6 per cent as moderate (2·5–4·5 cm) and 4 per cent as severe (more than 4·5 cm). All their patients had postoperative radiotherapy and were given active arm exercises the day after mastectomy. The results of the present trial are of the same order, but suggest that there is a significant increase in lymphoedema, at least to a slight degree, as a result of restriction of arm movement for 1 week postoperatively. Four months after discharge from hospital there was a mean increase of 3 mm in circumference of the upper arm and of 6 mm in the forearm. The reason for this is obscure, though reduced arm movements may lead to interference with the pumping action of the muscle on venous and lymph flow, and may promote axillary vein thrombosis. Guthrie and Gagnon (1946) advocated mobilization of the arm to prevent post-mastectomy lymphoedema, and noted a high incidence of swelling in those with poor function, but did not show which was cause and which effect.

With regard to shoulder mobility, it is generally advised that movements should be commenced early to prevent stiffness. Healey (1971), in a prospective study of 271 patients, found that 34 per cent had some limitation of shoulder movement 1–4 years after radical mastectomy, 8 per cent being unable to abduct to 90°. Some of them had performed early exercises under the supervision of a physiotherapist, others had had no formal instructions. Moreover, Pollard et al. (1976), in a study of 192 patients having both radical and simple mastectomy, found that early physiotherapy resulted in significantly better shoulder movements than were obtained in those patients advised not to move the arm until suture removal at 7–10 days. These patients, however, were not randomly allocated to the two treatment options. The present trial does not confirm that any increased shoulder stiffness results from limiting shoulder movement after operation.

It is concluded that active shoulder movement immediately after mastectomy should not be advised. Drainage is increased in volume and duration, without affecting eventual shoulder mobility. The liability to lymphoedema may be increased but is limited in extent.

Acknowledgements

I wish to express my thanks to Mr J. L. Hayward for his help and advice in performing this trial, and to the nursing staff of the Hedley Atkins Unit at New Cross Hospital. This study was undertaken during the course of an Imperial Cancer Research Fund Fellowship.

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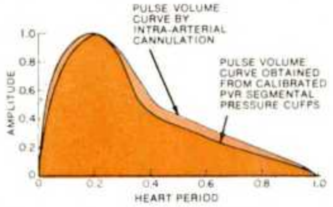

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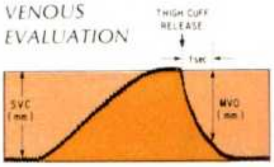

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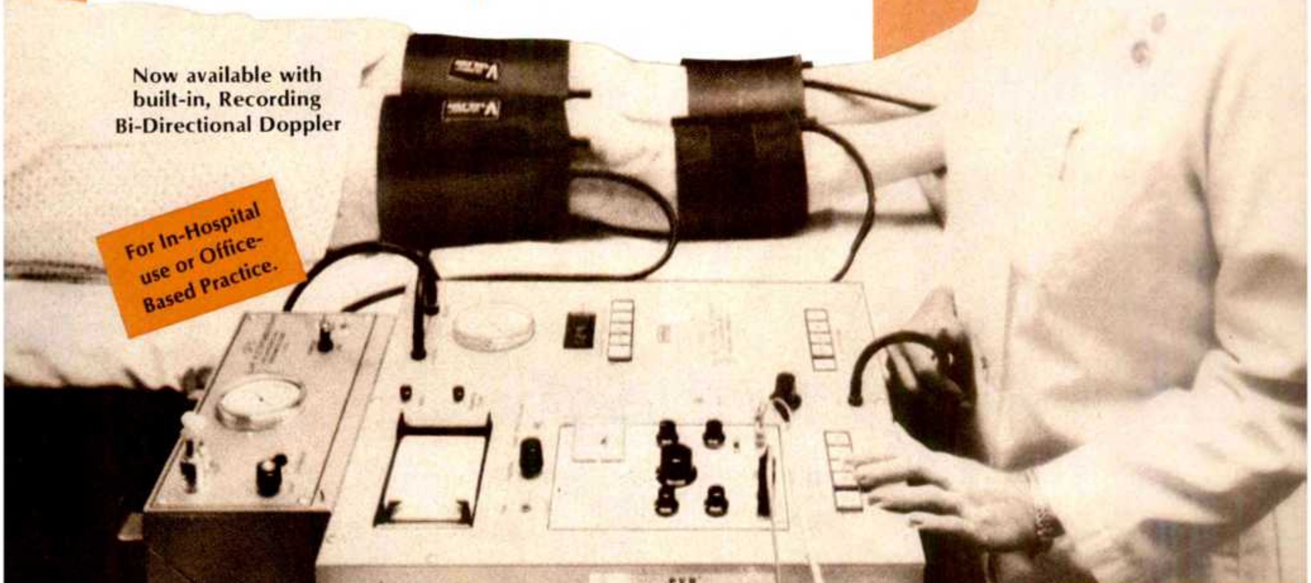

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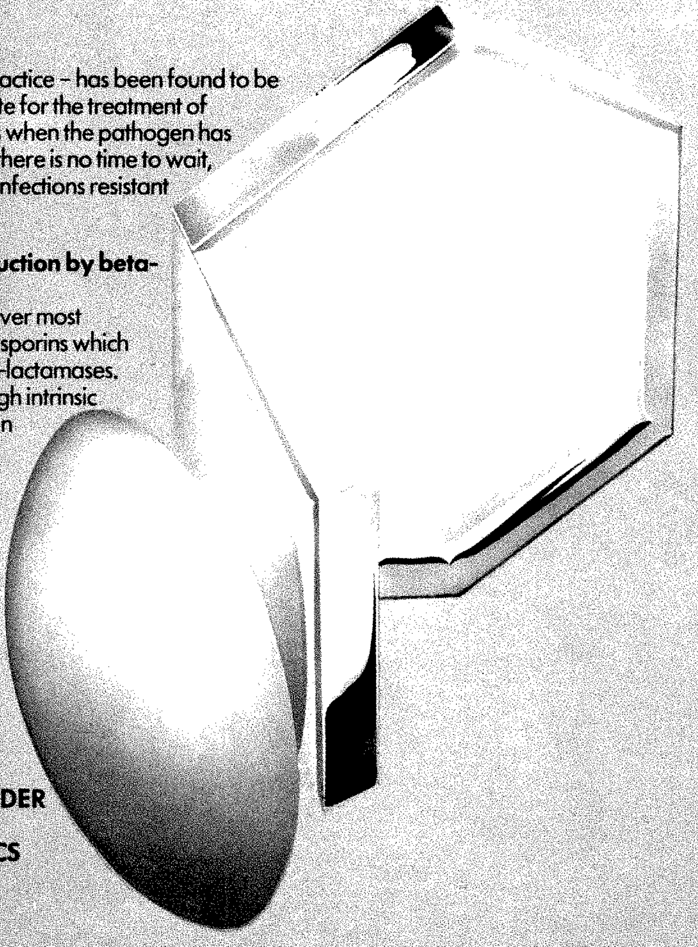

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References

ATKINS H., HAYWARD J. L., KLUGMAN D. J. et al. (1972) Treatment of early breast cancer: a report after ten years of a clinical trial. *Br. Med. J.* **2**, 423–429.

BOURKE J. B., BALFOUR T. W., HARDCASTLE J. D. et al. (1976) A comparison between suction and corrugated drainage after simple mastectomy: a report of a controlled trial. *Br. J. Surg.* **63**, 67–69.

EL-KHARADLY M. E. A. and ENEIN A. A. (1965) Post-mastectomy swelling of the arm. Review of the literature and preliminary report of 50 cases. *Br. J. Cancer* **19**, 30–38.

GUTHRIE D. and GAGNON G. (1946) Prevention and treatment of postoperative lymphoedema of arm. *Ann. Surg.* **123**, 925–936.

HEALEY J. E. JUN. (1971) Role of rehabilitation medicine in the care of the patient with breast cancer. *Cancer* **6**, 1666–1671.

KEYES E. L., HAWK B. O. and SHERWIN C. S. (1953) Basting axillary flap for wounds of radical mastectomy. *Arch. Surg.* **66**, 446–451.

LARSEN B. B. and HUGAN C. JUN. (1955) Fixation of skin flaps in radical mastectomy by subcutaneous sutures; observations. *Arch. Surg.* **71**, 419–423.

MORRIS A. M. (1973) A controlled trial of closed wound suction drainage in radical mastectomy. *Br. J. Surg.* **60**, 357–359.

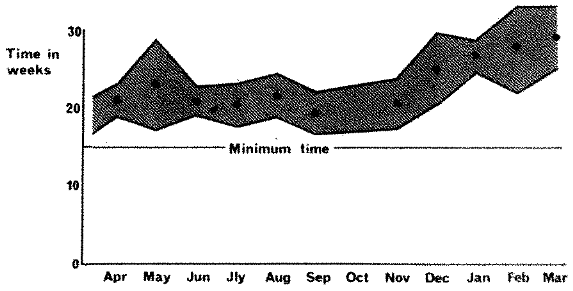
MURPHEY D. R. JUN. (1947) The use of atmospheric pressure in obliterating axillary dead space following radical mastectomy. *South. Surgeon* **13**, 372–375.

ORR T. G. (1951) Incision and method of wound closure for radical mastectomy. *Ann. Surg.* **133**, 565–566.

POLLARD R., CALLUM K. G., ALTMAN D. G. et al. (1976) Shoulder movement following mastectomy. *Clin. Oncol.* **2**, 343–349.

RIDDELL V. H. (1948) Radical mastectomy; the technique and the complications. *Br. J. Surg.* **36**, 113–129.

Paper accepted 17 November 1978.



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The management of suspected tumours of the colon: the role of colonoscopy in general surgery

S. T. D. McKELVEY*

SUMMARY

The role of colonoscopy in the management of 100 cases of suspected large bowel tumour is described. Forty out of 47 patients with an equivocal barium enema examination were satisfactorily examined and the possibility of a tumour being present was either confirmed or refuted. Examination of 30 patients with otherwise unexplained blood loss from the bowel revealed the cause in 50 per cent of them. Twenty-nine patients had pedunculated polyps which were snared and removed, thus avoiding laparotomy and colotomy.

The problem of distinguishing tumours from other lesions or retained faeces by radiology arises most often in the sigmoid colon. This segment is easily examined using a short flexible endoscope. General surgeons taking up colonoscopy will find a 1-m single-channel instrument convenient to use and capable of reaching approximately 90 per cent of colonic tumours that require further investigation or endoscopic resection. Facilities for the examination of the whole colon should be available in established endoscopy units.

FIBREOPTIC colonoscopy has not been widely practised by general surgeons in the United Kingdom because it is considered to be both difficult and time-consuming. Once the technique is mastered, however, colonoscopy often clarifies the diagnosis in colonic disease and may prevent an unnecessary laparotomy for suspected tumours (Hunt et al., 1975) or unexplained rectal bleeding (Waye, 1976; Teague et al., 1978). Colonoscopic polypectomy has transformed the management of patients with adenomatous polyps (Wolff and Shinya, 1973; Williams et al., 1974).

This paper presents the results of colonoscopy performed by a general surgeon in the investigation of patients with suspected large bowel tumours.

Patients and methods

One hundred patients with suspected large bowel tumours were examined. They were aged 20–86 years with a mean age of 56 years. There were 36 men and 64 women. The indications are given in *Table I*.

Patients were admitted 24 h before examination and put on a fluid diet. Except in frail patients, who were given a reduced dose, 142 mg of sennosides (X-Prep) were given orally in order to empty the colon. Two hours before the examination an enema of oxyphenisatin (Veripaque) was given. Each patient was given a premedication of diazepam, 10 mg orally, and most patients received a further 10 mg of diazepam and 50 mg pethidine intravenously before the endoscopy. Intramuscular cyclizine (50 mg) was given to minimize any nausea or retching. Three patients were examined under general anaesthesia.

Diagnostic colonoscopy was performed using single-channel instruments (ACMI Model F9L, Olympus Model CFMB3), while polypectomy was performed through a twin-channel endoscope (Olympus Model TCF2L). All examinations were carried out in the X-ray department using fluoroscopic control.

Table I: INDICATION FOR COLONOSCOPY IN 100 PATIENTS

Equivocal barium enema examination	47
Unexplained rectal bleeding	30
Polypectomy	23
Total	100

Table II: PATIENTS WITH EQUIVOCAL BARIUM ENEMA EXAMINATIONS (47 CASES)

Segment doubtful on X-ray	
Sigmoid colon	26
Sigmoid and descending colon	8
Descending colon	5
Transverse colon	3
Right colon	5
Total	47
Result	
Tumour excluded	31
Carcinoma confirmed	4
Polyps confirmed	5
Narrow stricture not entered	2
Failure to advance colonoscope	5
Total	47

Table III: UNEXPLAINED RECTAL BLEEDING IN 30 PATIENTS

Lesion	No. of cases
Polyps	5
Carcinoma	4
Inflammatory bowel disease	3
Diverticular disease	3
Radiation colitis	2
Rectal ulcer	1
Total	18

Table IV: POLYPECTOMY IN 33 PATIENTS

Referred for polypectomy	23
Referred with equivocal barium enema examination	5
Referred with rectal bleeding	5
	33
Outcome	
Polyps removed	29
'Polyps' not found	1
Malignant polyp—colectomy	1
Small polyps not fulgurated	2
	33

Results

Table II shows the results in 47 patients who had had an equivocal barium enema examination. In 26 patients the radiographs suggested the possibility of a carcinoma and polyps were suspected in the other 21 patients. In 40 out of the 47 patients it was possible to resolve the diagnostic problem by the finding of tumours in 9 and of a benign condition or a normal colon in 31. In 7 patients a diagnosis was not made; a narrow stricture which could not be entered was present in 2 patients and it was not possible to advance the instrument sufficiently in the other 5 patients. In 1 patient examined under a general anaesthetic a perforation occurred, which was recognized immediately and sutured at laparotomy.

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* The Royal Victoria Hospital, Belfast.

Examination of 30 patients with either frank rectal bleeding or anaemia due to blood loss showed a lesion in 18 patients; in the remaining 12 no colonic lesion was found (*Table III*). Patients with frank rectal bleeding gave a high yield, with positive findings in 16 out of 22 patients, although in 2 patients found to have diverticular disease and 1 patient with mild ulcerative colitis, a causal relationship between the pathology and the symptoms was doubtful. There were positive findings in only 2 out of 8 patients with occult bleeding. In one of these patients a pedunculated sigmoid polyp was removed and accepted as the cause. Two years later the patient was found to have a carcinoma of the transverse colon, despite a check barium enema examination 6 months after polypectomy.

Polypectomy was successful in 29 out of 33 patients (*Table IV*). Twenty-nine pedunculated polyps were snared and removed. In addition, 17 small sessile polyps were found and the majority of them were fulgurated. One patient had a malignant sigmoid polyp requiring colectomy. Six months after polypectomy in one patient, a further large polyp was found which had not been detected on the first occasion. The site of polyps removed is shown in *Fig.* 1.

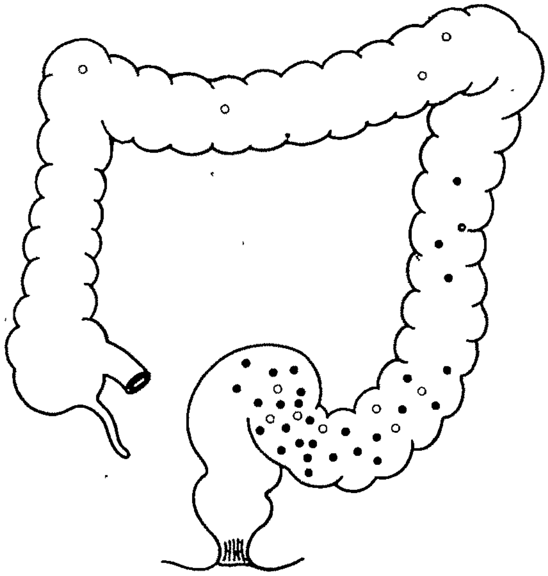

Fig. 1. The site of polyps removed in 29 patients. Pedunculated polyps are shown as closed circles and sessile polyps as open circles.

Discussion

Endoscopy of the colon may be considered as an extension of the practice of endoscopy of the rectum, which has been widely used by general surgeons. The technique of colonoscopy is relatively new and more difficult than that of sigmoidoscopy and this has inhibited its adoption in the management of colonic disease. As experience increases, and as improved instruments became available, it is probable that colonoscopy will be more widely used in the future.

In surgical practice colonoscopy is of most value in the management of patients with suspected tumours of the colon. The radiograph may show a lesion, suggestive of tumour, that is difficult to distinguish from benign disease or retained faeces. Sometimes the clinical problem is rectal bleeding not explained on proctosigmoidoscopy or after barium enema examination. If the radiology is technically satisfactory the surgeon can choose between colonoscopy or a laparotomy. The latter may produce equivocal findings and may result in an unnecessary operation.

Only 9 of the 40 patients in this series who were satisfactorily colonoscoped following an equivocal barium enema examination were found to have tumours. This suggests that clinicians were referring only very doubtful cases. Nevertheless, it is rewarding to be able to reassure the majority of patients that no tumour is present. The 2 patients who were found to have narrow strictures of the colon, which could not be entered, were submitted to laparotomy and had sigmoid colectomy for diverticular disease.

Rectal bleeding, the cause of which has not been demonstrated by sigmoidoscopy and barium enema examination, must be further investigated. In two-thirds of our patients with frank bleeding, colonoscopy revealed lesions that seemed to be the source of the bleeding. The discovery of a sigmoid carcinoma in 4 patients prompted a review of the previous investigations. In 3 of the 4 patients a single contrast enema had been performed in a peripheral hospital and the other had had a double contrast enema which had been carried out in a teaching hospital, although the appearances of the films suggested that inadequate bowel cleansing had been a major factor in obscuring the tumours. Colonoscopy for occult rectal bleeding is less productive but it may reveal important lesions in some patients (Waye, 1976). Teague and his co-workers (1978) emphasize the importance of total colonoscopy as the finding of a polyp in the distal colon may only have importance as a herald of a more proximal carcinoma. If the colon is normal, attention should be diverted to the stomach and small bowel.

Colonoscopic polypectomy represents a major advance over the traditional laparotomy/colotomy. The morbidity and mortality of colotomy are eliminated and the time off work required is reduced from 2–3 months to 2–3 days. In the 29 patients undergoing polypectomy in this series, no major complications arose, though in larger series a small incidence of haemorrhage and perforation is reported (Geenen et al., 1974; Graham and Eusebio, 1977). In one patient tenderness in the left iliac fossa was present for 72 h after fulguration of a small polyp with an insulated probe. The risk of full-thickness cautery can be avoided by the use of the hot biopsy technique (Williams, 1973) and all small sessile polyps can now be safely destroyed. Examination of at least the left colon, and perferably of the whole colon, should be carried out in conjunction with polypectomy as it is usual to find more polyps than were demonstrated by the barium enema examination.

The difficulties and dangers of colonoscopy cannot be lightly dismissed. Meticulous bowel preparation is essential, but this is no more than the requirement for good radiology. In this series, vigorous purgation with sennosides followed by an oxyphenisatin enema was found to be efficient, though sometimes distressing to the patient. Patients undergoing polypectomy should always be admitted for 48–72 h, but patients having examination only may be allowed home on the same day. Sedative and analgesic drugs, such as diazepam and pethidine, should be given, as most patients experience discomfort during the procedure.

Experience in handling upper gastrointestinal endoscopes is desirable before commencing colonoscopy, though there are problems in instrument insertion that are peculiar to colonoscopy. Passing the instrument from the sigmoid colon into the descending colon and around the hepatic flexure presents the most difficulty due to the great mobility of the sigmoid colon and the transverse colon. Various manoeuvres are described in the literature to overcome these difficulties (Williams and Teague, 1973). If problems persist, it is advisable to visit specialist centres or attend courses organized by the British Society of Digestive Endoscopy. Apprenticeship to an experienced colonoscopist would be ideal.

Major complications, such as full-thickness perforation, were reported in 0·9 per cent of a large series of patients (Geenen et al., 1974). Perforation is more likely to occur in the early experience of the colonoscopist, and when the examination is carried out under general anaesthesia. The endoscopist should aim to keep a view of the lumen at all times and should use the slide-by technique over short distances only. Pressure from the side of the instrument may cause stretching and possibly a tear of the apex of a large loop. These mishaps are unlikely to occur if the patient's complaint of pain is heeded, thus emphasizing the need to avoid the use of general anaesthesia. Polypectomy carries the additional risk of coagulation of the wall of the bowel and bleeding from the transected stalk. If the diathermy current is passed at a low setting at first and gradually increased until a band of coagulation appears which is equal in width to the diameter of the stalk, then bleeding is not likely to occur after separation. Coagulation of the bowel wall is prevented by not snaring too close to the base of the stalk and also by moving the position of the polyp between each short burst of current so that the opposite wall of the bowel is not damaged by current passing through the apex of the polyp. The coagulation of small sessile polyps is safe if a pseudopedicle is first created by pulling on the polyp using insulated biopsy forceps (Williams, 1973).

A long single-channel colonoscope is suitable for virtually all problems amenable to colonoscopy. However, as up to 90 per cent of 'surgical' problems are within reach of a short colonoscope (1 m), there is probably a case for the novice colonoscopist starting with a short single-channel instrument because it is easy to manipulate. A twin-channel colonoscope is helpful in polypectomy; it is sometimes more difficult to pass than a single-channel instrument, but has the advantage of leaving the suction channel free during snaring and allowing the polyp to be grasped before the stalk is completely severed.

General surgeons, whose main interest is gastroenterology, should use colonoscopy in the management of patients with large bowel disease. The increased accuracy in diagnosis and the ability to exclude carcinoma and remove polyps without laparotomy amply repay the expense and training required to master this rather difficult technique.

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References

GEENEN J. E., SCHMITT M. G. and HOGAN W. J. (1974) Complications of colonoscopy. *Gastroenterology* **66**, 812.

GRAHAM J. and EUSEBIO E. B. (1977) Complications of colonoscopy. *Illinois Med. J.* **152**, 39–42.

HUNT R. H., TEAGUE R. H., SWARBRICK E. T. et al. (1975) Colonoscopy in management of colonic strictures. *Br. Med. J.* **3**, 360–361.

TEAGUE R. H., THORNTON J. R., MANNING A. P. et al. (1978) Colonoscopy for investigation of unexplained rectal bleeding. *Lancet* **1**, 1350–1351.

WAYE J. D. (1976) Colonoscopy in rectal bleeding. *S. Afr. J. Surg.* **14**, 143–149.

WILLIAMS C. B. (1973) Diathermy-biopsy: a technique for the endoscopic management of small polyps. *Endoscopy* **5**, 215–218.

WILLIAMS C. B. and TEAGUE R. (1973) Progress report: colonoscopy. *Gut* **14**, 990–1003.

WILLIAMS C. B., HUNT R. H., LOOSE H. et al. (1974) Colonoscopy in the management of colon polyps. *Br. J. Surg.* **61**, 673–682.

WOLFF W. T. and SHINYA H. (1973) Polypectomy via the fibreoptic colonoscope. *N. Engl. J. Med.* **288**, 329–332.

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Cancer of the large bowel in a defined population: Canterbury, New Zealand, 1970–4

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SUMMARY

A total of 1024 new cases of cancer of the large bowel occurred in Canterbury, New Zealand (population 400 796), in the 5 years 1970–4. Of these, 992 were diagnosed before death and are reviewed in this paper.

The high incidence of this disease in New Zealanders of European origin is illustrated. A significant difference in site distribution of primary tumours between the sexes was found, with a female preponderance of cancer of the proximal colon gradually changing to a male preponderance of cancer of the rectum. In all, 61·5 per cent of the patients had lymph node metastases or advanced disease at the time of diagnosis or treatment. Largely as a consequence of this, only 65 per cent were able to have potentially curative treatment.

The estimated crude 5-year survival rate of the whole group was 32·7 per cent (relative rate 42·8 per cent) and the crude 5-year survival rate after potentially curative surgery was 48·4 per cent (relative rate 62·4 per cent).

The results are compared with those of other authors. They emphasize the generally unsatisfactory outcome of treatment.

It has been a conventional wisdom among doctors that large bowel cancer is a 'good tumour' which can often be cured by surgery. This attitude has been strengthened by relatively favourable reports of treatment based on the practice of special hospitals (Bussey and Morson, 1963; Wilson and Beahrs, 1976) or of individual surgeons (Morgan, 1965; Turnbull et al., 1974; Hughes, 1976). Nevertheless, as well as being the most prevalent major neoplasm in many Western countries (Higginson and Maclennan, 1973), the disease is drawing level with cancer of the lung as the major killer, at least in New Zealand (*New Zealand Health Statistics Report: Cancer Data*, 1976). Slaney (1971) showed that when a whole population is considered, the spectrum of disease and the results of treatment are less favourable than generally realized. Unfortunately, such population-based studies are uncommon and most reports concern the work of particular institutions where a variable and generally unknown degree of case selection has occurred.

The aims of this study are twofold. First, to survey cancer of the large bowel as it occurred recently in a defined Western population, with special reference to incidence, pathological spectrum, management and survival. Secondly, to give our students and colleagues an overview of the problem as it affects the people amongst whom they live and work.

Patients and methods

Most of the information contained in this paper came from the records of the National Cancer Registry (NCR), which is an organ of the National Health Statistics Centre, Department of Health. Abstracts of the records of cancer patients (except those with simple skin neoplasms) are forwarded to the registry by specially trained registrars based in the major public hospitals. The NCR estimates that the national registration rate was 92 per cent in 1971 and close to 100 per cent by 1974. However, in Canterbury it may have been somewhat better during this period, because of the centralized hospital service and the enthusiasm of the cancer registrars. The data are reviewed and further information is obtained from clinicians or pathologists if records are inconsistent or incomplete. In addition, the registry receives mortality returns from all death certificates. A fuller account of the activities of the NCR is given by Foster (1977).

The information was analysed with the aid of a PDP 11/70 digital computer. The following statistical methods have been used in this study: log rank test (LRT) (Peto and Pike, 1973), Kolmogorov–Smirnov two-sample test (K–S), Mann–Whitney U test (MWU) and the life-table method to calculate survival rates (Cutler and Ederer, 1958). In addition to crude survival rates, we have given, where appropriate, the relative survival rates (Ederer et al., 1961) defined as the percentage ratio of the crude survival rate for the patient group to the rate expected of people in the general population similar with respect to age, sex, race and period of observation. (This statistic is sometimes termed actuarial or corrected survival.) The 5 per cent level of significance has been adopted.

The population

The patients under study resided in the North Canterbury, Ashburton or South Canterbury Hospital Districts. This region approximates to the old Province of Canterbury, which is a natural geographical zone on the eastern side of the South Island of New Zealand. The population, as determined in the census of 1971, was 400 796, with 198 624 males and 202 172 females (*The New Zealand People 1971*, 1976). The age distribution is closely similar to that of the whole population of New Zealand and the hypothetical one proposed for European societies by Doll and Cook (1967).

Most Canterbury people are of European descent (95 per cent). The Polynesian community is smaller than in other parts of the country (3 per cent) and mostly consists of Maoris. Although New Zealand is an agricultural nation, 83 per cent of this population live in cities and towns, mostly in Christchurch, which had an urban population of 275 000 in 1971 There is significant mobility, with 32 per cent of the people having changed their address between the 1966 and 1971 censuses. However, this mostly occurred within the region and involved younger people.

Results

Incidence

In the 5-year period 1970–4, 1024 people were first diagnosed as having large bowel cancer. Of these, 25 cases were discovered at post-mortem and will be considered separately. A further 7 patients with carcinoid tumours of the appendix have been excluded because of the distinctive natural history of this disorder. This leaves 992 patients who were diagnosed before death. There were 607 cases of colonic cancer (261 men; 346 women), 347 cases of rectal cancer (201 men; 146 women) and 38 cases with cancer of the

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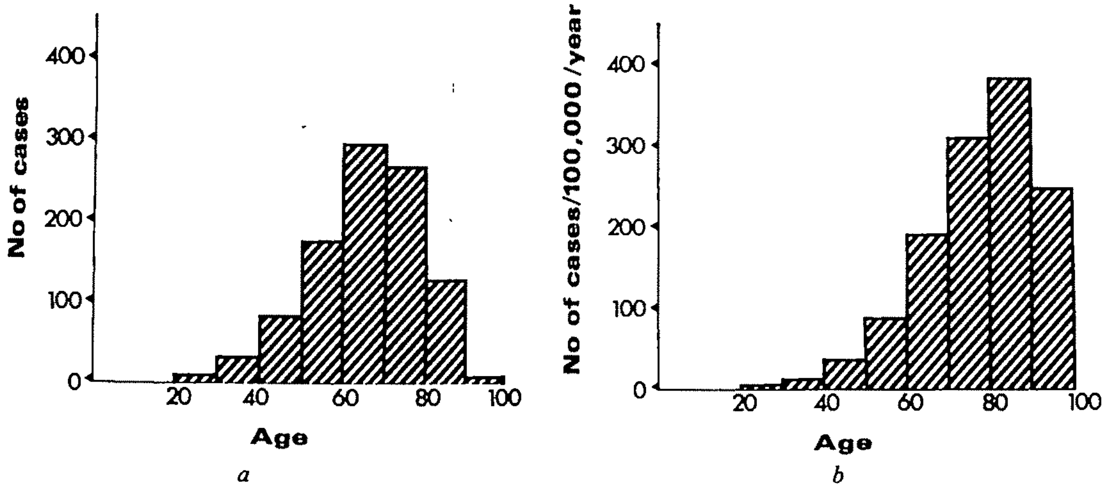

Fig. 1. *a*, The observed incidence of large bowel cancer in Canterbury by decade of life, compared with (*b*) the total number of cases by decade of life.

Table I: STANDARDIZED* INCIDENCE OF COLONIC AND RECTAL CANCER IN SEVERAL POPULATIONS

	Canterbury 1970–4	New Zealand† 1964–8	Connecticut† 1964–8	Birmingham† 1964–8	Denmark† 1964–8
Colon					
Male	24·1	24·7	26·7	15·3	15·5
Female	25·1	25·0	26·7	14·9	17·5
Rectum					
Male	18·6	15·6	16·3	15·8	17·2
Female	11·0	9·7	10·7	9·3	10·5

* According to method of Doll and Cook (1967) based on 'world' population of Segi (1960). Expressed as cases per 100 000 people per year.

† Rates given by Higginson and Maclennan (1973).

large bowel, site unspecified (22 men; 16 women). The overall incidence of large bowel cancer based on this series is 49·5 per 100 000 population per year.

Age-specific incidence: The incidence by decade of life is depicted graphically in *Fig.* 1 and compared with the total numbers by decade. It shows that incidence rises steeply with age, though the largest numbers of patients are aged between 60 and 70. The decline in incidence in the tenth decade is of uncertain significance for there were only 9 patients in this category.

Standardized incidence: Because age distribution often differs between populations (and between the sexes), the observed incidence may be misleading when used for comparisons. More reliable information can be obtained by using the standardized (age-adjusted) incidence (Doll and Cook, 1967), whereby the incidence is adjusted to that which would apply if the population had the age distribution of the hypothetical world population of Segi (1960). The standardized incidence per 100 000 per year by major site and sex based on this series is compared with some other populations in *Table I*. The figures illustrate the high incidence of large bowel cancer in New Zealand and suggest that there may be a higher rate of colonic cancer in New Zealand and North America than among some European populations.

Sex incidence: *Table I* also compares the incidence of colonic and rectal cancer in males and females. In each population given, the incidence of rectal cancer in men is substantially higher than that in women. In contrast, there is an equal incidence of colonic neoplasia (the greater numbers of females can be explained by their relative longevity).

Racial incidence: There was only one Maori patient in the group. The incidence of large bowel cancer in New Zealand Maoris is approximately 20 per cent of that among Europeans (*New Zealand Health Statistics Report: Cancer Data*, 1974). On this basis, one would have expected about 5 Maori patients.

Post-mortem diagnosis: Twenty-five patients were found, incidentally, to have large bowel cancer at post-mortem. In 1972, the national post-mortem rate was 31 per cent (*Trends: Health and Health Services*, 1975). The separate figures for Canterbury are not yet available. The total number of patients with unsuspected large bowel cancer may therefore have been approximately 80 in this 5-year period and inclusion of these cases in the incidence figures would increase them slightly.

Is the incidence changing? Some information on this is available on a national basis. The NCR uses a statistic called the standardized mortality ratio (SMR) which relates death rates from any cause to the respective rates applying in 1950–2. The mortality figures for large bowel cancer show no consistent change in the past 20 years (*New Zealand Health Statistics Report: Cancer Data*, 1974).

Pathology

Histology: Histological examination of the tumour was obtained in 922 of the 992 patients, i.e. 93 per cent. Of these, 96·5 per cent were adenocarcinomas, 2·5 per cent were carcinomas of unspecified type (our pathologists consider that these were mostly anaplastic adenocarcinomas), 0·9 per cent were squamous cell or basaloid carcinomas (all in the rectum or anal canal), and there was one leiomyosarcoma. Cytological grading was not recorded.

Site distribution: The sites of the primary tumours were classified according to the *International Classification of Diseases, Eighth Revision* (1967), except that site 153.8 (colon unspecified) and 153.9 (intestine unspecified) have been combined as 'large intestine unspecified', because of doubt about the way in which these categories were constituted. Most of such patients either had advanced disease or were incompletely documented.

The percentage distribution is illustrated in *Fig.* 2 and a significant difference between the sexes is shown (K–S, D = 0·172, $n_1 = 462$, $n_2 = 492$). There is a female predominance of cancer of the proximal colon which gradually changes to a male predominance of cancer of the rectum.

Unfortunately, the registration system did not allow for the recording of synchronous or metachronous primary tumours.

Stage of disease: The NCR stages large bowel cancer according to the following definitions:

Stage 1. Localized within the organ of origin.

Stage 2. Spread throughout the wall of the organ of origin but not into adjacent tissue (nodes not involved).

Stage 3. Regional spread with lymph node involvement.

Stage 4. Involving other organs or with distant metastases.

It will be appreciated that stages 1, 2 and 3 are similar to Dukes' stages A, B and C for rectal cancer (Dukes, 1932), but unfortunately are not defined in such a precise way.

Of the 992 patients, 951 were staged (i.e. 96 per cent). Most were staged pathologically, but some not having either surgical treatment or a post-mortem were staged clinically. There were 8·9 per cent with stage 1 lesions, 29·6 per cent with stage 2, 35·2 per cent with stage 3 and 26·3 per cent with stage 4 lesions. This means that over 60 per cent of the patients had lymph node metastases or advanced lesions at the time of diagnosis or treatment. There appeared to be a tendency for colonic tumours to be more advanced than rectal ones, but this did not achieve statistical significance (MWU, $Z = 1·95$).

Management

The generally accepted primary treatment for large bowel cancer is surgical excision. The surgeons in Canterbury adhere to this policy though they vary in such matters as the extent of associated lymphadenectomy. During the 5 years under study, there were 18 consultant general surgeons who undertook the bulk of the surgery, with registrars doing a smaller amount. Most of these operations were performed in 4 public hospitals (Christchurch, Princess Margaret, Ashburton and Timaru Hospitals) with a lesser number in 3 private hospitals (approximately 7 per cent in 1974).

Type of management: The types of management have been broadly classified as curative (when all known tumour was excised), palliative (when suspected or proved growth remained *in situ*) or no specific treatment. Of the 992 patients, 980 were classified in this way. Only 65 per cent of these were able to have potentially curative resections. Sixteen per cent had palliative procedures, most of which involved removal of the primary tumour and it is noteworthy that no bypass procedures or colostomies alone were recorded in the 5-year period. The overall resection rate was 79 per cent.

In *Tables II* and *III* the types of management for cancer of the colon and cancer of the rectum are given. The 38 patients with cancer of the large

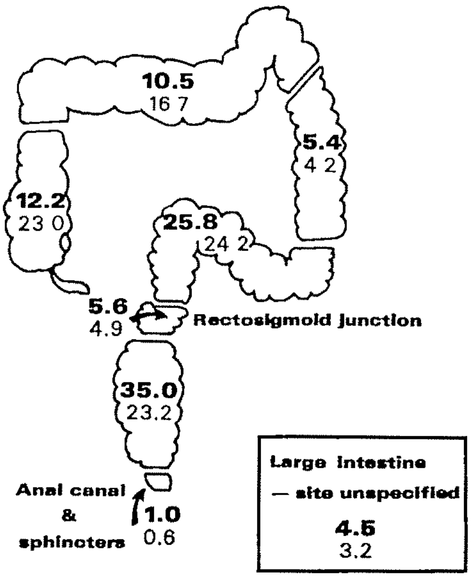

Fig. 2. Percentage distribution of primary tumours by site. Bold figures denote men, lighter figures, women.

Table II: MANAGEMENT OF COLONIC CANCERS IN 603 PATIENTS (99·3 PER CENT)

Curative	
Resection with anastomosis (one- or two-stage)	372
Resection with colostomy*	18
Unspecified surgery (presumed excisional)	6
	396 (65·7%)
Palliative	
Resection with anastomosis (one- or two-stage)	85
Resection with colostomy*	6
Unspecified surgery	1
Chemotherapy and/or radiotherapy	7
	99 (16·4%)
No specific treatment	108 (17·9%)

* Includes three-stage resection with anastomosis.

Table III: MANAGEMENT OF RECTAL CANCERS IN 345 PATIENTS (99·5 PER CENT)

Curative	
Abdominoperineal excision	150
Resection with anastomosis	77
Local excision	8
Unspecified surgery (presumed excisional)	3
	238 (69 0%)
Palliative	
Abdominoperineal excision	16
Resection with anastomosis	22
Local excision or fulguration	3
Unspecified surgery	8
Chemotherapy and/or radiotherapy	4
	53 (15·4%)
No specific treatment	54 (15 6%)

intestine (site unspecified) were managed in the following ways: curative treatment, 5; palliative treatment, 6; no treatment, 21; not known, 6. A total of 183 patients (i.e. 18·5 per cent of the whole group) received no specific treatment. The main reasons for this were: extent of disease (60 per cent), advanced age or poor general condition (27 per cent) and refusal of treatment (5 per cent).

Early mortality: Hospital or operative mortality was not recorded. However, knowing the number of people who died in the month of treatment and in the month following, we derived the upper and lower limits of the 1-month mortality rate. The mean of these two figures is our estimate of 1-month mortality. Arguably, this is a reasonable guide to hospital mortality. The 1-month mortality rate of the whole group of 992 patients was 12·8 (9·3–16·2) per cent. In the case of curative treatment the figures are 5·1 (3·4–6·7) per cent, for palliative treatment 11·7 (6·3–17·1) per cent and for no treatment 40·2 (31·7–48·6) per cent.

Survival

The survival data are accurate to the end of December 1975, because it takes up to 2 years for mortality returns to be received. Therefore, only patients treated in 1970 have been followed for 5 years. However, by using the life-table method we can give estimates of 5-year survival based on information about all the patients.

The crude 5-year survival rate for the whole group of 992 people is 32·7 per cent (s.e. mean = 1·9 per cent) and the relative survival rate is 42·8 per cent. In *Fig*. 3 the estimated crude survival curve is shown and compared with the survival curve of the general population with the same age–sex structure (*New Zealand Life-tables 1970–72*, 1975).

Factors influencing survival: The estimated survival by category of management is shown graphically in *Fig*. 4. Approximately half the patients having curative resections can be expected to survive for 5 years; the crude survival rate is 48·4 per cent (s.e. mean = 2·5 per cent) and the relative survival rate is 62·4 per cent. It is noteworthy that survival after curative resections was better for rectal cancer than for colonic cancer (rectum—crude 56·4 per cent, s.e. mean = 4·0 per cent, and relative 70·8 per cent; colon—crude 43·5 per cent, s.e. mean = 3·2 per cent, and relative 57·3 per cent). This difference was statistically significant (LRT, $\chi^2 = 6{\cdot}69$, d.f. = 1). We cannot explain this on the basis of differences in staging or age structure.

The 5-year survival rates for those undergoing palliative treatment or no treatment are not yet available. However, the crude 4-year rates are: palliative treatment 8·9 per cent (s.e. mean = 2·6 per cent); no treatment 2·8 per cent (s.e. mean = 1·3 per cent).

In previous papers good correlation has been demonstrated between survival and the extent of disease at the time of treatment (Bussey and Morson, 1963; Gill and Morris, 1978). The estimated survival curves relating to stage of disease for those patients who received either curative or palliative treatment are given in *Fig*. 5. The crude 5-year rates are: stage 1, 68·4 per cent (s.e. mean = 6·5 per cent); stage 2, 58·1 per cent (s.e. mean = 3·6 per cent); stage 3, 32·0 per cent (s.e. mean = 3·8 per cent); stage 4, not available,

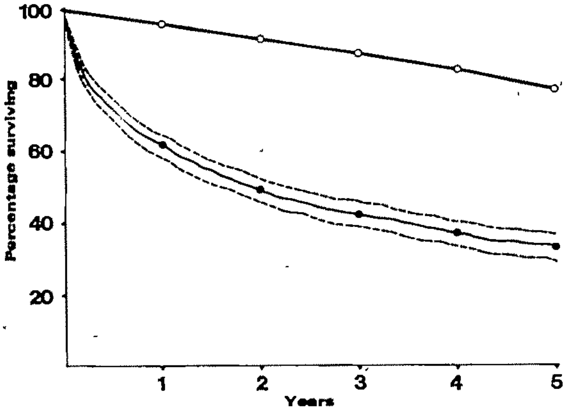

Fig. 3. Estimated crude survival curve for all patients (●——●) together with 95 per cent confidence limits (- - -), compared with survival curve of New Zealand population of same age–sex structure (○——○). (Drawn using 1-month increments.)

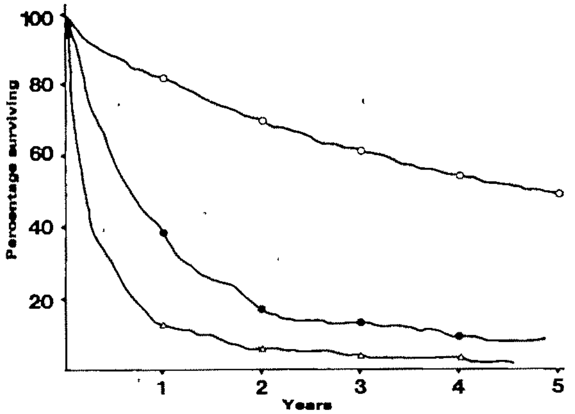

Fig. 4. Estimated crude survival curves for patients according to type of management. Curative treatment (○——○), palliative treatment (●——●), no treatment (△——△).

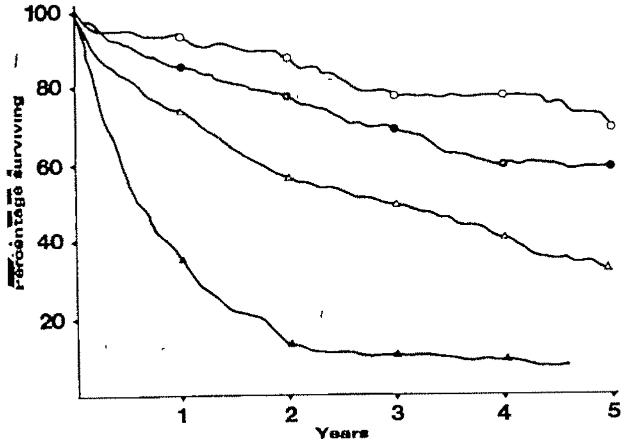

Fig. 5. Estimated crude survival curves for patients having either curative or palliative treatment according to stage of disease. Stage 1 (○——○), stage 2 (●——●), stage 3 (△——△), stage 4 (▲——▲).

Table IV: COMPARISONS OF TYPE OF MANAGEMENT AND SURVIVAL IN LARGE BOWEL CANCER

Series	Author(s)	Type	Number	% curative	% palliative	% no treatment	% 5-year survival Crude	% 5-year survival Relative
Birmingham region (1950–61)	Slaney (1971)	P	12 494	49	23	28	21	28
Malmo (1958–67)	Berge et al. (1973)	P	960	67	24	9	36	46
Canterbury (1970–4)	Present series	P	992	65	16	19	33	43
Charity, New Orleans (1948–60)	Floyd et al. (1966)	H	1248	39	n.g.	n.g.	23	n.g.
Radcliffe, Oxford (1966–71)	Gill & Morris (1978)	H	335	57	37	6	26	37
St Mark's (1948–62)	Hawley & Morson (1974)	SH	477 (colon)	n.g.	n.g.	n.g.	49	n.g.
St Mark's (1948–67)	Lockhart-Mummery et al. (1976)	SH	2410 (rectum)	ca. 75	ca. 20	ca. 5	47	57
Cleveland Clinic (1953–64)	Turnbull et al. (1974)	S	677 (colon)	70	15	15	n.g.	60
Melbourne (1966–70)	Hughes (1976)	S	549	74	n.g.	n.g.	40	n.g.

P, Population-based; H, hospital-based; SH, special hospital; S, individual surgeon; n.g., not given.

Table V: COMPARISON OF SURVIVAL AFTER CURATIVE RESECTIONS FOR RECTAL CANCER

Series	Author(s)	No.	% Dukes's A & B	% Dukes's C	% Operative mortality	% 5-year survival Crude	% 5-year survival Relative
Mayo Clinic (1959–69)*	Wilson & Beahrs (1976)	902	73	27	1·9	n.g.	72
St Mark's (1963–7)	Lockhart-Mummery et al. (1976)	434	57†	43†	2·1	60	72
Canterbury (1970–4)	Present series	238	55	45	5·1‡	56	71

* Includes sigmoid tumours.
† Based on period 1948–67.
‡ Estimated 1-month mortality.
n.g., Not given.

the 4 year-rate was 8·6 per cent (s.e. mean = 2·6 per cent).

It is planned to look in more detail at these and other factors that may influence survival when all patients have 'been in' for 5 years, at which time more accurate 5-year figures can be given and reasonable estimates of 10-year survival made.

Discussion

There were, unfortunately, a number of defects in the recording system used when these patients were registered. For example, there is no information about metachronous or synchronous tumours, the mode of presentation is not available and the classification of treatments is not particularly satisfactory. A new and more detailed method of registration, based on World Health Organization recommendations (*International Classification of Diseases for Oncology*, 1976) came into operation at the beginning of 1978. In addition, the NCR is becoming fully computerized. These changes should improve the scope and quality of available information in the future. However, in spite of these limitations, the series illustrates some important points.

First, the high incidence of large bowel cancer in New Zealand is well demonstrated. The rates for rectal cancer are similar in the several populations given in *Table I*, but there seems to be a substantially higher incidence of colonic cancer in New Zealand and North America than in Europe. This may be related to the finding in Connecticut, USA, that the incidence of tumours proximal to the rectosigmoid junction has increased in the past 30 years (Snyder et al., 1977). Another interesting finding is the difference in site incidence between the sexes. There is a higher incidence of proximal colonic cancer in women than in men and this gradually changes distally until, in the rectum, there is a higher incidence of cancer in men than women. An important consequence of this finding is that any theory about the cause of large bowel cancer should explain the substantial sex differences.

The series is similar to other population-based studies in that over 60 per cent of the patients had advanced disease or lymph node metastases at the time of diagnosis or primary treatment. Partly because of this, only 65 per cent were able to have surgery intended to cure them and the overall survival rates are poor. In *Table IV* we have compared some results recently reported from regions, hospitals or individual surgeons. The proportions of patients classified according to type of treatment are given, because such definitions tend to be more uniform than those for pathological staging systems. In any case, they reflect the extent of disease at the time of treatment. It can be appreciated from the Table that if suitable corrections were made for the differing compositions of the series, the survival figures might be very similar.

The point is better illustrated in *Table V*. Curative resections for cancers of the rectum at two specialized centres and in the Canterbury series are compared. Again, if one corrected for differences in staging and operative mortality, the 5-year survival figures would be almost identical. This suggests that the good results reported by special units largely depend on the spectrum of their practice.

In reviewing the literature on this subject, one has been disadvantaged by the lack of uniformity in presentation of results, especially of survival figures. This makes comparisons difficult. It is clear that some authors are less than completely frank about their results; for example, in one paper the only 5-year survival rate given was a *relative* one for the *survivors* of *curative* operations. Not surprisingly, it was over 70 per cent. We suggest that in future both crude and relative rates be given together, that operative mortality be included in these and that overall survival always be given as well as that of particular subgroups. In this way we will not lose sight of the generally unsatisfactory results of treatment.

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We thank our surgical colleagues in Christchurch, Timaru and Ashburton, for it is their work that we are reporting in this paper. We are indebted to Mr Frank Foster, Chief Health Statistician for New Zealand, and Mr J. Fraser and Miss J. Auld of the National Cancer Registry for access to the basic data and for critical suggestions about this paper. Dr A. McKinnon, Computer Scientist at the Christchurch Clinical School, also provided much help. The study was funded by the Robert McLelland Trust.

References

BERGE T., EKELUND G., MELLNER C. et al. (1973) Carcinoma of the colon and rectum in a defined population. *Acta Chir. Scand.* Suppl. 438, pp. 1–86.

BUSSEY H. F. R. and MORSON B. C. (1963) General results of surgical treatment of rectal cancer at St Mark's Hospital, 1928–1952. *Unio Internationalis Contra Cancrum Acta* 19, 1510–1513.

CUTLER S. J. and EDERER F. (1958) Maximum utilization of the life-table method in analysing survival. *J. Chronic Dis.* 8, 669–712.

DOLL R. and COOK P. (1967) Summarizing indices for comparison of cancer incidence data. *Int. J. Cancer* 2, 269–279.

DUKES C. E. (1932) The classification of cancer of the rectum. *J. Pathol. Bacteriol.* 35, 323–332.

EDERER F., AXTELL L. M. and CUTLER S. J. (1961) *The Relative Survival Rate. A Statistical Methodology.* Bethesda, National Cancer Institute, pp. 101–121. (National Cancer Institute, Monograph No. 6.)

FLOYD C. E., STIRLING C. T. and COHN I. (1966) Cancer of the colon, rectum and anus: review of 1,687 cases. *Ann. Surg.* 163, 829–837.

FOSTER F. H. (1977) The New Zealand cancer registry. *N.Z. Med. J.* 86, 341–343.

GILL P. G. and MORRIS P. J. (1978) The survival of patients with colorectal cancer treated in a regional hospital. *Br. J. Surg.* 65, 17–20.

HAWLEY P. R. and MORSON B. C. (1974) Cancer of the colon. Aetiology, pathology, diagnosis: prognosis of cancer of the colon. In: MAINGOT R. (ed.) *Abdominal Operations*, 6th ed. New York, Appleton–Century–Crofts, pp. 1920–1935.

HIGGINSON J. and MACLENNAN R. (1973) The world pattern of cancer incidence. In: RAVEN R. (ed.) *Modern Trends in Oncology, 1. Part 1: Research Progress.* London, Butterworths, pp. 9–28.

HUGHES E. S. R. (1976) Long-term study of large-bowel cancer. *Med. J. Aust.* 2, 365–368.

INTERNATIONAL CLASSIFICATION OF DISEASES, EIGHTH REVISION (1967). Geneva, World Health Organization.

INTERNATIONAL CLASSIFICATION OF DISEASES FOR ONCOLOGY (1976). Geneva, World Health Organization.

LOCKHART-MUMMERY H. E., RITCHIE J. K. and HARVEY P. R. (1976) The results of surgical treatment for carcinoma of the rectum at St Mark's Hospital from 1948 to 1972. *Br. J. Surg.* 63, 673–677.

MORGAN C. N. (1965) Carcinoma of the rectum. *Ann. R. Coll. Surg. Engl.* 36, 73–97.

NEW ZEALAND HEALTH STATISTICS REPORT: CANCER DATA (1974) Wellington, New Zealand Department of Health.

NEW ZEALAND HEALTH STATISTICS REPORT: CANCER DATA (1976) Wellington, New Zealand Department of Health.

NEW ZEALAND LIFE-TABLES 1970–72 (1975) Wellington, New Zealand Department of Statistics.

PETO R. and PIKE M. C. (1973) Conservatism of the approximation $\Sigma\ (O-E)^2/E$ in the log rank test for survival data or tumor incidence data. *Biometrics* 29, 579–584.

SEGI M. (1960) *Cancer Mortality for Selected Sites in 24 Countries (1950–1957)* Sendai, Department of Public Health, Tohoku University School of Medicine.

SLANEY G. (1971) Results of treatment of carcinoma of the colon and rectum. In: IRVINE W. (ed.) *Modern Trends in Surgery, 3.* London, Butterworths, pp. 69–89.

SNYDER D. N., HESTON J. F., MEIGS J. W. et al. (1977) Changes in site distribution of colorectal carcinoma in Connecticut, 1940–1973. *Am. J. Dig. Dis.* 22, 791–797.

THE NEW ZEALAND PEOPLE 1971 (1976) Wellington, New Zealand Department of Statistics.

TRENDS· HEALTH AND HEALTH SERVICES (1975) Wellington, New Zealand Department of Health.

TURNBULL R. B., KYLE K., WATSON F. R. et al. (1974) Cancer of the colon: the no-touch isolation technique of resection. In: MAINGOT R. (ed.) *Abdominal Operations*, 6th ed. New York, Appleton–Century–Crofts, pp. 2018–2028.

WILSON S. M. and BEAHRS O. H. (1976) The curative treatment of carcinoma of the sigmoid, rectosigmoid, and rectum. *Ann. Surg.* 183, 556–565.

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Angiodysplasia as a cause of colonic bleeding in the elderly

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SUMMARY

Angiodysplasia is being recognized as a major causal factor of colonic haemorrhage in the elderly. Superior mesenteric arteriography in an 86-year-old lady with recurrent haemorrhage revealed the lesion. Confirmation of the diagnosis was made possible by the injection of contrast material into the blood vessels of the removed intestine and subsequent histological examination.

ANGIODYSPLASIA in the right colon has, in recent times, become recognized as one of the most important causal factors of haemorrhage from the large bowel in the elderly. These vascular malformations of the digestive system are difficult to detect either by endoscopy or by barium meal examination. Selective arteriography of the superior mesenteric artery is the most valuable diagnostic tool.

Case report

An 86-year-old woman, known to be suffering from aortic stenosis and mild heart failure, was admitted with rectal bleeding in October 1975. Endoscopy and barium meal examinations failed to reveal the source of the bleeding. After blood transfusion the bleeding abated.

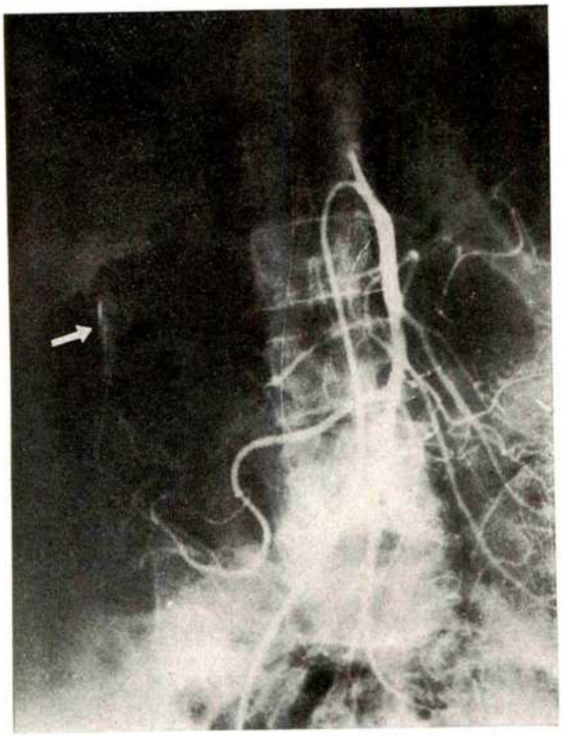

Fig. 1. Superior mesenteric arteriography showing early venous phase, with leak of contrast material into the lumen of the ascending colon (arrow).

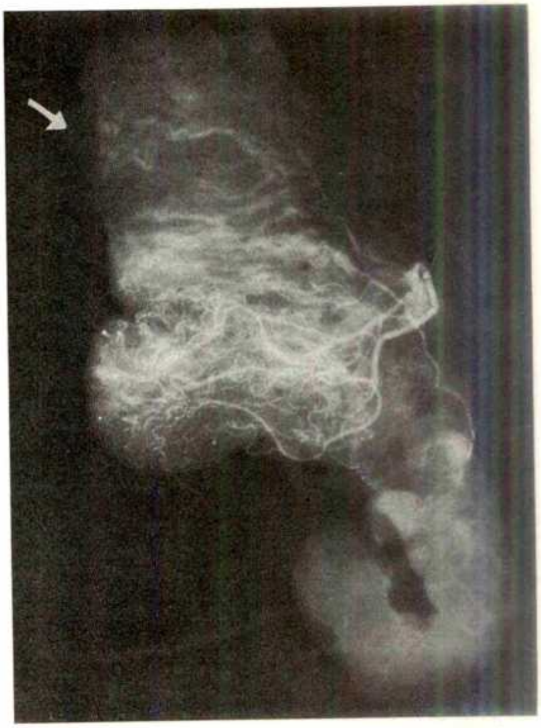

Fig. 2. Radiograph of the excised specimen showing the arteries, which are injected with radio-opaque material. The arrow shows the area of angiodysplasia from which histological sections were taken.

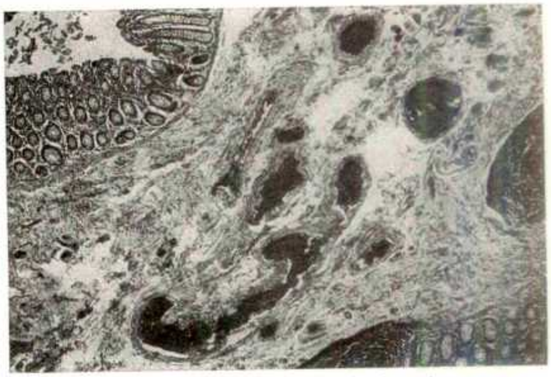

Fig. 3. Showing dilated vascular lakes in the submucosa, which are characteristic of angiodysplasia. (× 80).

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In February 1977 the patient was readmitted with severe rectal bleeding, and at this time a polyp was found in the sigmoid colon. It was suspected that this was the cause of the bleeding and a sigmoid colectomy was performed.

Two months later the patient was again admitted with recurrent rectal bleeding. At this time selective arteriography of the superior mesenteric artery revealed a leak of contrast material into the lumen of the ascending colon (*Fig.* 1). The bleeding persisted and a right hemicolectomy was performed. Her postoperative course was uneventful and she was reviewed in the follow-up clinic. At her last visit in July 1978 the patient, now in her eighty-ninth year, was free of any further rectal bleeding.

The diagnosis of angiodysplasia was confirmed by injection of barium diluted with Gastrografin into the blood vessels of the resected colon (*Fig.* 2). Arteriovenous malformations were demonstrated, and microscopic examination showed clusters of dilated blood vessels, which took the form of contrast-filled lakes in the submucosa (*Fig.* 3).

Discussion

It has recently become apparent that angiodysplasias or vascular ectasias are responsible for colonic bleeding as frequently as diverticulosis in the elderly (Cooperman and Kelly, 1972; Margulis and Castelman, 1974; Crichlow et al., 1975; Moore et al., 1976; Boley et al., 1977; Hagihara et al., 1977; Marx et al., 1977; Welch et al., 1978).

Margulis et al. in 1960 first demonstrated by arteriography the extravasation of contrast material into the intestinal lumen during active bleeding. Baum et al. (1972) initially described the pathological features of this disease, which have been further elucidated by Boley et al. (1977). The lesions are arteriovenous fistulas or aneurysms that penetrate the muscularis mucosa and are seen as submucosal vascular lakes. The aetiology of these lesions is not certain but several theories exist.

Heyde (1958) found a statistical association of aortic stenosis and gastrointestinal bleeding and Williams (1961) surveyed 1443 cases of gastrointestinal bleeding at the Massachusetts General Hospital and found that there was a 25·5 per cent relationship with aortic stenosis. However, Marx et al. (1977) discounted this relationship.

Baum et al. (1975) attributed these vascular malformations to a submucosal leak occurring during periods of hypotension.

Boley et al. (1977) have suggested that the lesions may be caused by long term, low grade obstruction of the submucosal venules, especially where they pierce the muscular layers of the bowel. This results in retrograde dilatation of these venules, and when there is finally loss of the function of the precapillary sphincters, small arteriovenous fistulas are produced. Diagnosis is made by selective arteriography. During active bleeding there may be extravasation of contrast medium into the lumen of the bowel. This, however, occurs only if the bleeding is brisk. Pathognomonic signs are the accumulation of contrast material in vascular tufts during the capillary phase. The venous phase shows early filling of large veins, indicating arteriovenous fistulas. The arterial phase is normal.

If the lesion is detected, a right hemicolectomy is performed, since the natural history of these lesions is one of recurrent bleeding. Welch et al. (1978) report that in 12 per cent of patients who underwent only a segmental colectomy, rebleeding occurred. Boley et al. (1977) note that rebleeding is rare after right hemicolectomy.

The identification of the lesions by the pathologist may be difficult unless the 'coral head' appearance of advanced angiodysplasia is seen (Boley et al., 1977). In order to localize the lesions, the vessels of the excised intestine were first injected with a mixture of barium in Gastrografin. The specimen was then X-rayed, revealing the area of angiodysplasia. In this way it was possible to localize the lesion and take accurate specimens for histological examination.

Angiodysplasia is not known to be a major cause of colonic bleeding in the elderly. In these patients the use of arteriography and the performance of a right hemicolectomy will greatly improve the prognosis.

References

BAUM S., ATHANASOULIS C. A., WALTMAN A. C. (1972) Paper presented at the 58th Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago Ill. (Abstr. 181.)

BAUM S., ATHANASOULIS C. A., WALTMAN A. C. et al. (1975) Angiodysplasia of the right colon as a cause of chronic gastrointestinal bleeding. *Gastroenterology* **68**, 682.

BOLEY S. J., SAMMARTANO S., ADAMS A. et al. (1977) On the nature and etiology of vascular ectasias of the colon: degenerative lesions of aging. *Gastroenterology* **72**, 650–660.

COOPERMAN A. M. and KELLY K. A. (1972) Arteriovenous malformations of the intestine. An uncommon cause of gastrointestinal bleeding. *Arch. Surg.* **104**, 284–287.

CHRICHLOW R. W., MOSENTHAL W. T., SPEIGEL P. K. et al. (1975) Arteriovenous malformations of the bowel. An obscure cause of bleeding. *Am. J. Surg.* **129**, 440–443.

HAGIHARA P. F., CHUANG V. P. and GRIFFEN W. O. (1977) Arteriovenous malformations of the colon. *Am. J. Surg.* **113**, 681–686.

HEYDE E. C. (1958) Gastrointestinal bleeding in aortic stenosis. *N. Engl. J. Med.* **259**, 196.

MARGULIS A. R. and CASTELMAN B. (1974) Case records of the Massachusetts General Hospital (Case 36, 1974). *N. Engl. J. Med.* **291**, 569–571.

MARGULIS A. R., HEINBECKER P. and BERNARD H. R. (1960) Operative mesenteric arteriography in the search for the site of bleeding in unexplained gastrointestinal hemorrhage. *Surgery* **48**, 534–539.

MARX F. W., GRAY R. K., DUNCAN A. M. et al. (1977) Angiodysplasia as a source of intestinal bleeding. *Am. J. Surg.* **134**, 125–130.

MOORE J. D., THOMPSON N. W., APPLEMAN H. D. et al. (1976) Arteriovenous malformations of the gastrointestinal tract. *Arch. Surg.* **111**, 381–388.

WELCH C. E., ATHANASOULIS C. A. and GADABINI M. D. (1978) Hemorrhage from the large bowel with special reference to angiodysplasia and diverticular disease. *World J. Surg.* **2**, 73–83.

WILLIAMS R. C. (1961) Aortic stenosis and unexplained gastrointestinal bleeding. *Arch. Intern. Med.* **108**, 859–864.

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Extra-intracranial revascularization

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SUMMARY

Twenty-four extra-intracranial revascularization procedures were undertaken in 23 patients with occlusion of the ipsilateral internal carotid artery. The superficial temporal artery was anastomosed to a cortical branch of the middle cerebral artery in 23 cases and a vein graft inserted between the external carotid artery and the cortical vessel in 1, a microsurgical technique being used.

Twenty-one patients were suffering from transient ischaemic attacks (TIAs) and 2 had developing strokes. Nineteen patients had radiologically demonstrated bilateral disease of the carotid vessels, 9 having undergone contralateral carotid artery surgery before the intracranial procedure.

No improvement was noted in the 2 patients with developing strokes; one patient developed a stroke contralateral to the intracranial procedure 24 h postoperatively, this being accompanied by occlusion of the anastomoses, and one patient had progression of the stroke syndrome following occlusion of the intracranial vein graft. All other patients have shown a reduction or abolition of TIAs over a follow-up period of 24 months.

These findings suggest that intracranial revascularization is of value in patients with total internal carotid artery occlusion and continuing TIAs.

THE role of reconstructive surgery in the extracranial portion of the carotid system for patients with stroke syndromes is now well established (Taylor and Lumley, 1977a, b). The usual pathology is a stenotic lesion of the common carotid bifurcation and the presenting symptoms are those of recurrent motor or sensory TIAs affecting the appropriate hemisphere or amaurosis fugax. In a small proportion of patients the internal carotid artery becomes totally occluded and in this situation the chances of restoring patency are higher with early operation but so are the risks of haemorrhage into a recent infarct (Bruetman et al., 1963; Blaisdell et al., 1969).

Some patients survive a total occlusion of the internal carotid artery without the development of a major stroke but later suffer from TIAs appropriate to the ischaemic hemisphere. The long term prognosis is poor in this group, Ziegler and Hassanein (1973) reporting a 45 per cent incidence of major strokes within a 3-year period. In 1968, Donaghy and Yasargil gave a preliminary report of a new technique of revascularizing the intracerebral vessels by means of a superficial temporal to middle cerebral artery (ST–MCA) bypass using microsurgical techniques. Lougheed et al. (1971) studied the possibilities of grafting on to the intracranial portion of the internal carotid artery, but surgeons have generally favoured the originally described ST–MCA anastomoses. A number of reports have now appeared in the overseas literature as to the efficacy of this procedure for patients with the stroke syndrome (Yasargil et al., 1970; Reichman et al., 1972; Austin et al., 1974; Yonekawa and Yasargil, 1976; Chater 1976a, b; Holbach et al., 1976; Sundt et al., 1976) and more recently reports have been published from British centres (Lumley, 1976, 1978; Bannister, 1977). This paper discusses the first 24 procedures undertaken by the Surgical Professorial Unit at St Bartholomew's Hospital, the longest follow-up being 24 months.

Patients and methods

The presenting symptoms, angiographic findings and operative details of the 23 patients are summarized in *Table I*. Referrals were initially from neurologists in 15 cases, ophthalmic surgeons in 2 and peripheral vascular clinics in 3 cases.

Twenty-one of the 23 patients were male and all were right-handed; their average age was 59·6 years and the average length of history was 19·3 months. The term 'TIA' in *Table I* has been used to indicate all reversible neurological episodes, which were of the prolonged variety in only 2 patients. Visual episodes reported in the Table are amaurosis fugax unless stated to the contrary. Dysphasia is not subdivided. As psychological tests with a Halstead–Reitan battery were only performed on some of the patients, the reported memory and mental changes represent description by the patient or close relatives. The number of neurological episodes was 3 or less in 7 patients and in excess of 20 in 6 patients.

The blood pressure readings presented are from the right upper limb at the time of the intracranial procedure; there was no marked variation from left arm pressures in any patient. Angiographic assessment included bilateral carotid arteriography by direct stab or selective catheterization techniques. Angiographic findings were those of arteriosclerosis in all patients, this diagnosis being confirmed histologically in the 11 patients undergoing carotid artery surgery in the neck.

In *Cases* 12, 17 and 21, the internal carotid artery was occluded distal to its ophthalmic branch. In *Cases* 2, 5 and 11 the internal carotid artery on the side of the intracerebral anastomosis was not occluded at the time of arteriographic assessment. In *Cases* 2 and 11, however, there was minimal backflow from the internal carotid at the time of initial exploration and in view of radiologically demonstrated thrombus in the carotid syphon in *Case* 2 and severe distal stenosis in *Case* 11, the internal carotid artery was disconnected and the origin of the external carotid artery rebored and refashioned in each case. In *Case* 5, although the internal carotid artery was patent at the time of angiography, it had occluded by the time of exploration in the neck.

The first intracranial procedure was undertaken on 18 April 1976, the last being performed on 21 April 1978.

Surgical technique

The aim of the operative procedure is to provide an additional arterial blood supply to the cerebral hemisphere beyond an occluded internal carotid artery. In the absence of serious neurological defects the cortical branches of the middle cerebral artery are usually patent and one or more of these branches are used to introduce a new blood supply. The superficial temporal artery over the temporal region is of equivalent size to a cortical vessel. If the blood flow in this artery is unimpaired it is divided and the proximal end anastomosed end to side on to the cortical vessel using microsurgical techniques. In 9 patients a frontoparietal skin flap was raised, the superficial temporal artery being dissected on a fascial pedicle from the deep surface of the flap. In the other cases the artery was mobilized through a skin incision over it.

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Table 1: CLINICAL DETAILS AND PROGRESS OF PATIENTS

Case no./ Age (yr)	Length of history	Presenting symptoms	No. of neuro-logical episodes	Blood pressure (mmHg)	Daily cigarettes/ tobacco	Other features
1/53	15 mth	L stroke, mild residual weakness, +motor TIAs. Mild dysphasia. R motor TIAs. 2 focal left-sided epileptiform attacks	9+	180/110	40	Alcoholic
2/53	1 wk	Dysphasia. R motor + sensory mild stroke. L amaurosis fugax symptoms gradually increasing	3	120/70	3	Mother died of myocard infarction
3/59	2½ yr	Blackouts. BL multiple visual TIAs with progressive visual loss. BL motor TIAs. R sensory TIAs	20+	200/120	20, none 2 yr	On methyldopa
4/65	6 mth	Near complete recovery of L stroke 8 yr before. L visual TIAs with some permanent loss. R motor TIAs. Memory deterioration	6	165/80	20	Claudication 200 yd 4 yr
5/52	1 yr	Memory deterioration. BL motor+sensory TIAs	9+	140/80	40	Hypercholesterolaemia. Brother died of myocardial infarction
6/64	1 yr	Dysphasia. Marked memory deterioration; unable to go out alone. R motor+visual TIAs	20+	130/90	40	Angina, myocardial infarc claudication 400 yd 8 y Polycythaemia
7/70	6 mth	Dizziness. R visual TIAs	20+	160/100	20	On methyldopa
8/60	1 yr	Dysphasia. Progressive memory deterioration. Mild persistent R paresis	2	180/100	15	Claudication 1 mile 6 yr
9/61	2½ yr	Mental deterioration. Dizziness. R visual TIAs. L sensory TIAs	9+	140/70	25	Claudication 120 yd. Previous alcoholic
10*/51	18 mth	Disturbances of consciousness + psychiatric treatment followed by dense R paresis. Slow recovery with marked depression + lack of spontaneous activity	10	170/110	½ oz 20 yr	Slight increase triglyceride Claudication 1000 yd 2 yr
11/70	26 mth	Dysphasia. R motor + BL visual TIAs. Mentally slow	20+	180/90	30 18 yr, none 15 yr	Hypertension treated with diuretics. Claudication
12/60	48 mth	Dysphasia. Residual mild R paresis. Mild L face + arm paresis. R visual TIAs progressing to blindness	9	215/115	10	Myocardial infarct. On methyldopa. Previous aorto-iliac surgery. Sister has arterial disea
13/67	12 mth	L motor TIAs. Developing L dense paresis at time of surgery	5	140/70	30 10 yr, 3 oz/wk	On propanolol
14/59	3½ yr	R TIAs proceeding to marked paresis with dysphasia. Slow recovery. L hand sensory loss. Dizziness + BL blurring of vision	20+	180/80	4	
15*/51	22 mth	Disturbances of consciousness + psychiatric treatment followed by dense R paresis. Slow recovery with marked depression + lack of spontaneous activity	10	170/110	½ oz 20 yr	Slight increase triglyceride Claudication 1000 yd f 2 yr
16/53	6 wk	R visual TIAs. L motor TIAs and mild paresis of face	2	130/70	30 40 yr	Myocardial infarct
17/57	4 d	Progressive L hemiparesis	1	130/80	20	
18/70	36 mth	Dizziness. R motor + sensory TIAs	20+	110/80	25 53 yr	Angina. Permanent pacin On methyldopa

(Table continues)

Presenting radiological findings	Intracranial anastomosis	Carotid surgery prior to intracranial procedure		Progress
		Contralateral	Ipsilateral	
ICA occlusion, L ICA severe stenosis, both at origin + in syphon	R ST-MCA Apr. 1976	IC and ECA endart., 11 mth		Anticonvulsants restarted because of 3 further fits. No motor deterioration. Still alcoholic
ICA, marked stenosis at origin with free thrombus at origin + in syphon. R ECA moderate stenosis + supraclinoid ICA disease	L ST-MCA May 1976		Ligation of ICA and endart. ECA 1 wk	Improvement of speech. No further motor or visual deterioration
ICA occlusion. R ICA marked stenosis at origin	L ST-MCA Aug. 1976	IC and ECA endart., 6 mth		Temporary dysphasia after carotid and intracranial procedures. 12 L visual TIAs. No motor TIAs
ICA occlusion. L CCA occlusion. L vertebral 50% stenosis	R ST-MCA Oct. 1976			Two R motor TIAs, otherwise unchanged
L ICA, marked stenotic disease of origins and syphons	L vein graft EC-MCA Jan. 1977	IC and ECA endart., 7 mth	ECA endart. 1 yr. L subclavian-ECA vein graft 1 wk	Two L motor TIAs
ICA occlusion. L ECA 50% stenosis at origin+ICA syphon disease	R ST-MCA Mar. 1977			Marked improvement of memory; able to go out alone. No further TIAs
ICA occlusion. L ICA syphon disease	R ST-MCA Mar. 1977			Asymptomatic
ICA occlusion. L ICA marked stenosis at origin + in syphon	R ST-MCA May 1977	IC and ECA endart., 1 mth		Some speech improvement, otherwise no change
ICA occlusion. L ICA marked disease at origin + in syphon	R ST-MCA May 1977	IC and ECA endart. 3 wk		Marked improvement of mental state. 2 R visual TIAs
L CCA occlusion	R ST-MCA Oct. 1977		Subclavian-ECA vein bypass 2 wks	Less depressed and more active at home. Paresis continuing to improve
R ICA severe stenosis into skull + ECA origin stenosis. L CCA + ICA syphon stenosis	R ST-MCA Nov. 1977		Exploration ligation CCA + ECA endart. 1 wk	No further symptoms
R ICA marked stenosis proximally + occlusion distal to the ophthalmic branch. L ICA syphon stenosis	R ST-MCA Nov. 1977			Walking without preoperative stick and some improvement in fine movements L hand
R ICA occlusion	R ST-MCA Jan. 1978			Persistence of dense L paresis
L ICA occlusion. R ICA and ECA stenosis	L ST-MCA Jan. 1978	IC and ECA endart., 42 mth		No change
BL CCA occlusion	L ST-MCA Feb. 1978	Subclavian-ECA vein bypass 4½ mth; ST-MCA bypass 4 mth	Subclavian-ECA vein bypass consecutively	Less depressed and more active at home. Paresis continuing to improve
R ICA occlusion. Slight irregularity L carotid vessels	R ST-MCA Feb. 1978			No further TIAs
R ICA near complete occlusion with clot up to syphon with no filling of intracranial vessels	R ST-MCA Feb. 1978			Persistence of dense left paresis. Fatal R stroke 6 wk postop.
R ICA occlusion. L ICA occlusion + ECA stenosis	R ST-MCA Mar. 1978			No further TIAs

(Table continues)

Table 1: *cont.*—

Case no./ Age (yr)	Length of history	Presenting symptoms	No. of neuro-logical episodes	Blood pressure (mmHg)	Daily cigarettes/ tobacco	Other features
19/61	13 mth	Loss of recent memory. R homonomous hemianopia. EMI scan showed L occipital infarct with cerebral atrophy		210/100		Claudication
20/67	7 mth	L visual TIAs. Dysphasia. R motor TIAs each increasing a a mild residual arm paresis	6	120/90	20/wk 38 yr	
21/56	14 mth	L motor TIAs. Dysphasia. Mild R paresis	3	120/100	1 oz	Claudication 300 yd. Increased pre-β-lipoproteins. Positive WR. On guanethidine and oxprenol
22/64	36 mth	R visual TIAs. R hand mild weakness	5+	130/70	18	Angina
23/62	48 mth	R hemiparesis, slow progress to near complete recovery. L paresis, good recovery. Dyslexia. Dysgraphia. Dysphasia. Dizziness	2	200/150	None	Reaction to hypotensive drugs
24/46	15 wk	L motor TIAs and mild residual arm paresis. L mild sensory loss. Headache. Blackouts.	2	150/90	20 15 yr, none 9 mth	Diabetes. Hyperlipidaemia

Times relate to the intracerebral procedure.
ECA, External carotid artery. CCA, Common carotid artery. ICA, Internal carotid artery. MCA, Middle cerebral artery. ST, Superficial temporal artery. L, Left; R, right; BL, bilateral. WR, Wassermann reaction. endart., endarterectomy.
* Cases 10 and 15 are the same patient undergoing two procedures.

The bony approach was centred 6 cm superior and 1 cm posterior to the external auditory meatus, a separate vertical skin incision being used when a flap was not raised. Initially a craniotomy was used, but a craniectomy was subsequently made, a single burr hole being enlarged as necessary.

The dura mater was incised in stellate fashion, and an adjacent parietal or angular branch of the middle cerebral artery was mobilized for the anastomosis. The anastomosis was fashioned with interrupted 10/0 monofilament nylon using a Zeiss operating microscope. Systemic heparin was used in *Case* 5 where an external carotid artery to middle artery vein bypass was being inserted. Prophylactic antibiotics were administered for 1 week and phenobarbitone was prescribed as an anticonvulsant over the operative period and for 3 weeks postoperatively. The latter medication was reintroduced 4 months later in *Case* 1 when this patient had three focal epileptiform attacks. Dipyridamol and aspirin were administered to the later patients in the series.

Results

Postoperative progress is summarized in *Table I*. Patency of the anastomosis was assessed by digital and Doppler examinations of the superficial temporal artery. The vein graft in *Case* 5 failed after 3 months and the ST–MCA bypass failed in *Case* 20 (it is not known whether this occurred immediately before or after his stroke). A weak Doppler signal is present to near the burr hole in 3 cases and patency is questionable, but the remainder are considered patent on Doppler and clinical testing. Cerebral blood flow was also studied by different isotope techniques at three centres. In *Case* 1 postoperative angiography of the anastomosis was undertaken at 3 weeks and 12 months (*Figs*. 1, 2), but routine postoperative angiography has not been performed.

There were no recurrent postoperative motor TIAs recorded contralateral to the intracerebral anastomosis, however established weakness on this side was not markedly altered, of particular note being the persistent paresis in the 2 patients with developing strokes (*Cases* 13 and 7). *Case* 17 developed a terminal stroke ipsilateral to the ST–MCA anastomosis 4 weeks after the procedure. *Case* 20 was operated upon as an emergency after two episodes of dense but transient motor paresis, but the operation did not prevent the onset of a dense paresis 24 h later. Mental improvement in *Cases* 6, 9 and 10 (15), while not recorded quantitatively, was subjectively marked as assessed by patients and relatives. *Cases* 1 and 9, although of employable age, have not returned to full employment; both have been under psychiatric care for long term alcoholic problems.

Discussion

The incapacity and other consequences of stroke on a patient and those close to him make the search for means of prevention an important medical priority. Initial progress in the field was stimulated by the realization that major strokes were often preceded by TIAs and the disease process was often in the surgically accessible extracranial arteries (Eastcott et al., 1954). Treatment of patients with an occluded internal carotid artery in its inaccessible portion by ST–MCA bypass was pioneered by Donaghy and Yasargil (Donaghy, 1967; Yasargil, 1969a, b).

All the patients in the present series were suffering from arteriosclerosis; this predominance has also been present in other series although the use of extra–intracranial bypass has been advocated in a variety of other diseases (Reichman, 1975; Chater and Popp, 1976; Sundt et al., 1976; Yonekawa and Yasargil, 1976). All except 2 of the patients had motor, sensory or visual TIAs or persistent neurological symptoms related to an occluded internal carotid artery. The

Presenting radiological findings	Intracranial anastomosis	Carotid surgery prior to intracranial procedure		Progress
		Contralateral	Ipsilateral	
ICA occlusion. R CCA stenosis near termination + marked stenosis of ICA origin	L ST–MCA Mar. 1978			No change
ICA occlusion	L ST–MCA Mar. 1978			R stroke 24 h postop.
ICA occlusion distal to ophthalmic branch. R ICA occlusion 3 cm from origin	L ST–MCA Mar. 1978			No further TIAs
ICA occlusion, stenosis origin innominate. R ICA occlusion 1 cm from origin	L ST–MCA Mar. 1978			No further TIAs
ICA occlusion. R ICA + ECA stenosis + subclavian irregularity	L ST–MCA Mar. 1978	IC and ECA endart., 24 mth		No change
ICA occlusion. L ICA and ECA marked stenosis at origins	R ST–MCA Apr. 1978	IC and ECA endart., 7 wk		No change

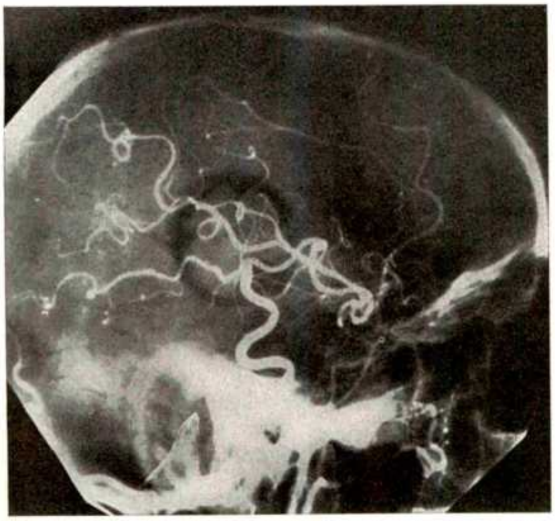

Fig. 1. *Case* 1. Lateral view of the right superficial temporal to middle cerebral artery bypass. Selective right common carotid arteriogram undertaken 1 year after the bypass operation.

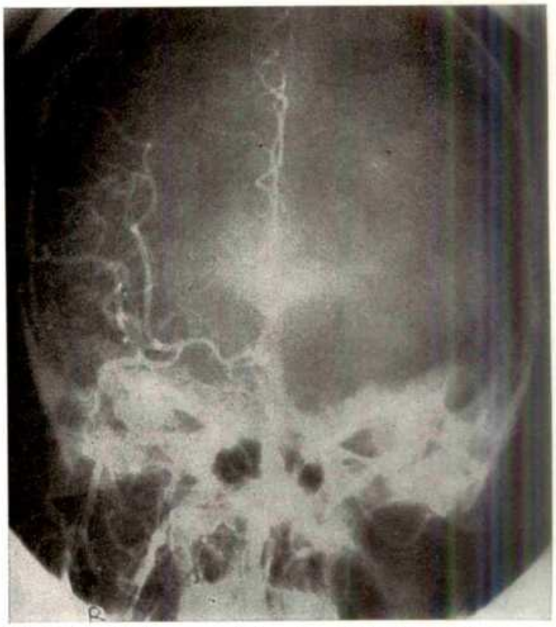

Fig. 2. *Case* 1. Anteroposterior view of the bypass shown in *Fig.* 1.

marked reduction of TIAs is encouraging. Yonekawa and Yasargil (1976) reported a 75 per cent relief of symptoms while Chater and Popp (1976) reported a 92 per cent relief from or substantial reduction of TIAs.

The most disappointing result in the present series was that in *Case* 20, where it was hoped that recent motor TIAs of increasing severity could be abolished. It is not known whether the occlusion of the ST–MCA bypass in this patient preceded or followed the stroke he developed 24 h postoperatively, or indeed whether the operation precipitated the event. The bypass operation undertaken in 2 patients with developing strokes did nothing to reverse the established neurological deficit, although it could be argued that there was no further contralateral deterioration in either case. One of these patients suffered an ipsilateral progressive stroke; this was the only death in the series. These results in the patient with developing stroke do not encourage the use of cerebral revascularization in this particular group. Chater and Popp (1976) did note an improvement in 5 patients who presented with progressive deterioration of the neurological status but no improvement in patients with moderate or severe persistent neurological deficits.

The absence of late strokes in the group is encouraging but has to be judged in the light of the limited follow-up period. Chater (1976b), on analysis of his follow-up, showed that there was a 3 per cent postoperative incidence of strokes related to the area supplied by the bypass and in one of these 3 cases the stroke accompanied occlusion of the bypass. The overall incidence of strokes in his series was 7 per cent, this including strokes referable to the non-operated hemisphere. Chater estimated from the results of Whisnant et al. (1973) that there would have been a 22 per cent incidence of strokes in the same group of patients if they had been treated conservatively. Operative mortality in Chater's group was 1·4 per cent.

The mental improvement seen in the present series is difficult to interpret in the absence of objective testing, although striking to local observers. These findings are consistent with those of Perry et al. (1975) and of Ferguson and Peerless (1976), who advocated the use of intracranial revascularization in patients with dementia related to widespread cerebrovascular disease.

The arteriographic techniques in the present series were partly dependent on the preference of the referring physician. It is essential to obtain adequate information on the intracranial circulation in patients presenting with TIAs in order to exclude the presence of tumours, angiomas and aneurysms as well as to assess the extent of the arterial disease. This information can be obtained by direct carotid puncture or by selected injections from the aortic arch. Arch aortography is indicated when vertebrobasilar insufficiency or an associated subclavian steal are being investigated. Selective carotid arteriograms, however, require more elaborate apparatus, the use of larger volumes of contrast media and take longer to perform than direct stab techniques.

The widespread nature of the arterial disease seen in this series is also reflected in other reports. Yonekawa and Yasargil (1976) reported a 37 per cent incidence of bilateral internal carotid artery occlusion while Sundt et al. (1976) described a 15 per cent incidence of bilateral disease.

When considering the surgical techniques, some surgeons raise a skin flap and a branch of the superficial temporal artery is dissected from its deep surface (Yasargil et al., 1970; Chater and Peters, 1976; Sundt et al., 1976; Yonekawa and Yasargil, 1976). The incidence of flap necrosis reported after this method ranged from 2 to 10 per cent (Chater, 1976a; Sundt et al., 1976). One patient in the present series had delayed healing of a scalp flap. Primary union was obtained in all cases where the superficial temporal artery was mobilized by an incision directly over it. In no case in the present series was it necessary to use the occipital artery for bypass. In the one case requiring a vein graft the occipital and superficial temporal artery were both inadequate. The value of vein grafts in this area still requires careful study.

Although a 1-cm burr hole is large enough to undertake an ST–MCA anastomosis, as the adequacy of the adjacent cortical arteries cannot be predicted before the dural incision, it is usual to make a 3–5-cm craniectomy. In this series the parietal or angular branch of the middle cerebral artery was used for anastomosis as advocated by Chater and his associates (Chater and Peters, 1976; Chater and Popp, 1976; Chater et al., 1976). The largest available cortical vessel was chosen while avoiding damage to perforating branches. Through a small craniectomy it is often not possible to distinguish the angular branch from parietal branches. Yonekawa and Yasargil (1976) advocated the use of a temporal branch of the middle cerebral complex while Reichman and his associates (Reichman, 1975; Reichman et al., 1972, 1974, 1975), although willing to use any branch of the middle cerebral complex, aimed to place the anastomosis over the area at risk. A rich anastomosis has been reported between the branches of the middle cerebral artery (Feindel, 1970), and temporary occlusion of a cortical vessel does not appear to lead to permanent ischaemic damage. Heparin is ill-advised in neurosurgery, it has not been advocated in intracranial revascularization and, in the one case where it was administered systemically in the present series, continued oozing proved difficult to control and greatly hindered the completion of the anastomosis.

Technical details of microsurgery, such as the degree of magnification, the type of arterial clamp, the method of incising the cortical vessel, the incision and placing of the superficial temporal artery, the use of stents and of dams and the order of stitching, differ considerably between surgeons. The most important factor, however, is that the operator should gain considerable preliminary experience in microvascular surgical techniques in small animal research.

The routine use of anticonvulsants is not universal. Yonekawa and Yasargil (1976) reported an 8 per cent incidence of postoperative fits but they withheld treatment until a fit manifested itself. Antiplatelet drugs such as dipyridamol and aspirin have not been advocated routinely in this field but, from experience in other microvascular techniques and on theoretical grounds, they would appear to be of value.

The determination of the patency of the ST–MCA anastomosis in the early and later postoperative period is not as easy to assess as might be supposed. If one can palpate the superficial temporal artery into the craniectomy, the vessel is probably functioning. At this site, however, it is usually covered by the temporalis muscle and fascia and is difficult to palpate. Presence of a palpable superficial temporal artery in the pre-auricular area may indicate anastomotic patency but may also be related to filling of another branch. The Doppler probe is a useful tool and, where the vessel diameter has been recorded, an estimated superficial temporal artery flow can be obtained by this means (Sundt et al., 1976). Carotid arteriography by selective or carotid stab techniques carries with it a small morbidity and in the initial postoperative phase may fail to demonstrate a patent anastomosis. This is thought to be due to slow flow in the superficial temporal artery, perhaps related to initial oedema and spasm, or possible failure to time exposures correctly. The value of cerebral blood flow measurement using various isotopic techniques is still under investigation in the present series.

A distinct learning curve was reported by Sundt et al. (1976) when assessing graft patency. These authors reported 25 per cent patency in initial studies but 99 per cent patency in more recent procedures. Yonekawa and Yasargil (1976) reported an 85 per cent patency in their series as assessed mainly arteriographically while Chater and Popp (1976) reported a 95 per cent graft patency when assessed by Doppler ultrasound.

Postoperative progress in these patients is smoother than it often is after carotid artery surgery in the neck, where there can be marked instability of blood pressure in the postoperative period (Angell-James and Lumley, 1974).

The results of this series confirm the findings of others, earlier in the field, that extra–intracranial revascularization procedures can carry a low morbidity and mortality even though undertaken in a high risk group of patients. Follow-up in this series shows a marked reduction in TIAs while long term results in the existing literature suggest that the procedure is of value in stroke prevention. It appears that this form of surgery can take its place alongside carotid endarterectomy as a means of prophylaxis in the treatment of the stroke syndrome. Patients with an occluded internal carotid artery and TIAs should be treated by intracerebral revascularization before the development of irreversible neurological deficits. The procedure requires meticulous surgical techniques and adequate training in both microvascular and neurosurgical fields.

References

ANGELL-JAMES J. E. and LUMLEY J. S. P. (1974) The effects of carotid endarterectomy on the mechanical properties of the carotid sinus and carotid sinus nerve activity in atherosclerotic patients. *Br. J. Surg.* **61**, 805–810.

AUSTIN G., LAFFIN D. and HAYWARD W. (1974) Physiological factors in the selection of patients for superficial temporal artery into middle cerebral anastomosis. *Surgery* **6**, 861–868.

BANNISTER C. M. (1977) Superficial temporal–middle cerebral artery anastomosis in patients with reversible cerebral ischaemic episodes. *J. R. Coll. Surg. Edinb.* **22**, 136–141.

BLAISDELL W. F., CLAUSS R. H., GALBRAITH J. G. et al. (1969) Joint study of extracranial vascular occlusion. IV A review of surgical considerations. *JAMA* **209**, 1889–1895.

BRUETMAN M. E., FIELDS W. S., CRAWFORD E. S. et al. (1963) Cerebral haemorrhage in carotid artery surgery. *Arch. Neurol.* **9**, 458–467.

CHATER N. (1976a) Surgical results and measurements of intraoperative flow in microneurosurgical anastomoses. In: AUSTIN G. M. (ed.) *Microsurgical Anastomoses for Cerebral Ischaemia.* Springfield, Ill., Thomas, pp. 295–304.

CHATER N. (1976b) Patient selection and results of extra- to intracranial anastomosis in selected cases of cerebrovascular disease. *Clin. Neurosurg.* **23**, 287–309.

CHATER N. and PETERS N. (1976) Neurosurgical microvascular bypass for stroke. *West. J. Med.* **124**, 1–5.

CHATER N. and POPP J. (1976) Microsurgical vascular bypass for occlusive cerebrovascular disease: review of 100 cases. *Surg. Neurol.* **6**, 115–118.

CHATER N., SPETZLER R. and TONNEMACHER K. (1976) Anatomical localization of optimal middle cerebral branch for anastomosis. In: AUSTIN G. M. (ed.) *Microsurgical Anastomosis for Cerebral Ischaemia*, Springfield, Ill., Thomas, pp. 39–51.

DONAGHY R. M. P. (1967) Patch and bypass in microangional surgery. In: DONAGHY R. M. P. and YASARGIL M. G. (ed.) *Microvascular Surgery.* St Louis, Mosby, pp. 75–86.

DONAGHY R. M. P. and YASARGIL M. G. (1968) Extra-intracranial blood flow diversion. In: Proceedings of the American Association of Neurological Surgeons. Chicago, Ill.

EASTCOTT H. H. G., PICKERING G. W. and ROB C. G. (1954) Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. *Lancet* **2**, 994–996.

FEINDEL W. H. (1970) Intracerebral vascular anatomy. In: Proceedings of the American College of Surgeons. Chicago, Ill.

FERGUSON G. G. and PEERLESS S. J. (1976) Extracranial–intracranial bypass in the treatment of dementia and multiple extracranial arterial occlusion. In: Proceedings of a joint meeting on stroke and cerebral circulation, Dallas, Texas.

HOLBACH K.-H., WAPPENSCHMIDT J. and BODOSI M. (1976) Angiographische Befunde bei extra–intrakraniellen Anastomosen. *Radiologe* **16**, 416–423.

LOUGHEED W. M., MARSHALL B. M., HUNTER M. et al. (1971) Common carotid to intracranial internal carotid bypass venous graft. *J. Neurosurg.* **34**, 114–118.

LUMLEY J. S. P. (1976) Intracerebral revascularization. In: Proceedings of the International College of Surgeons. London.

LUMLEY J. S. P. (1978) Extra–intracranial revascularization. *Ann. R. Coll. Surg.* (*Engl.*) **60**, 139

PERRY P. M., DRINKWATER J. E. and TAYLOR G. W. (1975) Cerebral function before and after carotid endarterectomy. *Br. Med. J.* **4**, 215.

REICHMAN O. H. (1972) Continued patency of canine lingual–basilar system. *Stroke* **3**, 586–591.

REICHMAN O. H. (1975) Extracranial–intracranial arterial anastomosis. In: WHISNANT J. P. and SANDOK B. A. (ed.) *Cerebral Vascular Disease.* New York, Grune & Stratton, pp. 175–185.

REICHMAN O. H., ANDERSON R. E., ROBERTS T. S. et al. (1975) The treatment of intracranial occlusive cerebrovascular disease by STA-cortical MCA anastomosis. In: HANDA H. (ed.) *Microneurosurgery.* Tokyo, Igaku Shoin, pp. 31–46.

REICHMAN O. H., DAVIS D. O., ROBERTS T. S. et al. (1974) Anastomosis between STA and cortical branch of MCA for the treatment of occlusive cerebrovascular disease. In: MEREI F. T. (ed.) *Reconstructive Surgery of Brain Arteries.* Budapest, Hungarian Academy of Science, pp. 201–218.

REICHMAN O. H., SATOVICK R. M., DAVIS D. O. et al. (1972) Collateral circulation to the middle cerebral territory by anastomosis of superficial temporal and cortical arteries. In: FUSEK I. and KUNC Z. (ed.) *Present Limits of Neurosurgery.* Prague, Avicenum, pp. 369–373.

SUNDT T. M., SIEKERT R. G., PEIPGRAS D. G. et al. (1976) Bypass surgery for vascular disease of the carotid systems. *Mayo Clin. Proc.* **51**, 677–692.

TAYLOR G. W. and LUMLEY J. S. P. (1977a) Surgery for strokes. In: TAYLOR S. (ed.) *Recent Advances in Surgery.* Edinburgh, Churchill Livingstone, pp. 395–422.

TAYLOR G. W. and LUMLEY J. S. P. (1977b) Extracranial surgery for vascular disease. *Adv. Tech. Standards Neurosurg.* **4**, 15–41.

WHISNANT J. P., MATSUMOTO N. and ELVEBACK L. R. (1973) Transient cerebral ischaemic attacks in a community; Rochester, Minnesota, 1955 through 1969. *Mayo Clin. Proc.* **48**, 194–198.

YASARGIL M. G. (1969a) Diagnosis and indications for operations in cerebrovascular occlusive disease. In: YASARGIL M. G. (ed.) *Microsurgery Applied to Neurosurgery.* Stuttgart, Thieme, pp. 95–119.

YASARGIL M. G. (1969b) Anastomosis between the superficial temporal artery and a branch of the middle cerebral artery. In: YASARGIL M. G. (ed.) *Microsurgery Applied to Neurosurgery.* Stuttgart, Thieme, pp. 105–115.

YASARGIL M. G., KRAYENBUHL H. A. and JACOBSEN J. H. (1970) Microsurgical arterial reconstruction. *Surgery* **67**, 221–233.

YONEKAWA Y. and YASARGIL M. G. (1976) Extra–intracranial arterial anastomosis. Clinical and technical aspects. Results. *Adv. Tech. Standards Neurosurg.* **3**, 37–78.

ZIEGLER D. K. and HASSANEIN R. S. (1973) Prognosis in patients with transient ischaemic attacks. *Stroke* **4**, 666–673.

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Deep vein thrombosis after total hip replacement: a clinical and phlebographic study

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SUMMARY

Two hundred and forty-seven phlebograms (113 bilateral and 21 unilateral) were performed in 134 patients 10-14 days after total hip replacement. Fifty-eight per cent of the patients were found to have deep vein thrombosis. The patients with DVT were significantly older than patients without DVT, but there was no difference regarding sex, type of hip prosthesis, side of operation or day of mobilization. No difference was found in the duration of operation and anaesthesia, the operative haemorrhage and the amount of bank blood transfused in patients with and without DVT.

Fifty per cent of the thrombi were confined to the calf veins. Ninety-seven per cent of these thrombi were asymptomatic and were as frequent on the operated as on the non-operated side. The remaining 50 per cent of the thrombi engaged the thigh with or without simultaneous calf vein involvement. These thrombi produced symptoms in 23 per cent of the cases and were significantly more common on the operated than on the non-operated side.

It is concluded that DVT after hip replacement can be of two different types: thrombosis caused by stasis and the general effects of trauma and thrombosis caused by local factors involving the thigh veins of the operated leg.

DEEP vein thrombosis (DVT) is a common postoperative complication (Kakkar et al., 1969). The pattern of DVT after hip surgery differs in several respects from that seen in general surgery. The incidence of DVT after hip surgery is considerably higher (Evarts and Feil, 1971; Hampson et al., 1974). Iliofemoral thrombi are common, and thrombi in the thigh often occur isolated from DVT in the calf (Harris et al., 1977). Factors reputed to contribute to the high incidence of thrombi after hip surgery include advanced age, prolonged postoperative bed rest and major trauma to the tissues with activation of the coagulation system (Sevitt and Gallagher, 1961; Walsh et al., 1976). Manipulation of the leg in connection with total hip replacement with intraoperative distortion and occlusion of the femoral vein has also been claimed to be a cause of DVT (Stamatakis et al., 1976).

The aim of the present investigation was to study the location and frequency of various types of postoperative deep vein thrombi and to evaluate the importance of various factors connected with hip operations in the development of postoperative DVT.

Patients and methods

The material consisted of 134 patients with osteoarthritis of the hip who had total hip replacements performed during the period of May 1975 to May 1977. All patients were given dextran 70 (Macrodex 6 per cent in saline, Pharmacia AB, Sweden) as a thromboembolic prophylaxis. Preoperative normovolaemic haemodilution with dextran 70 was performed in 54 patients. This haemodilution was performed as follows. After induction of anaesthesia, but before the operative procedure, haemodilution was performed by replacing blood with dextran to lower the haematocrit to 25-30. The volume of the drained blood was substituted by the same volume of dextran to maintain normovolaemia. The technique of preoperative haemodilution in total hip replacement has been previously described in detail (Ahlberg et al., 1977). The remaining 80 patients were given 500 ml of dextran 70 during the operation (starting after induction of anaesthesia) and on the second postoperative day. Age, sex, type of hip prosthesis and side of operation are presented in *Table I*.

Table I: CLINICAL MATERIAL

Mean age	
66±8 yr	
Sex	
Male	50
Female	84
Hip prosthesis	
Charnley	54
Brunswick	74
Other	6
Side of operation	
Right	80
Left	54
Total	134

For all patients the following variables were recorded: time of operation and anaesthesia; operative haemorrhage, calculated from operative bleeding and from suction drains postoperatively; amount of bank blood transfused during operation and postoperatively; day of mobilization (walking with weight bearing).

All patients had phlebograms performed 10-14 days postoperatively. No special effort was made to diagnose deep vein thrombosis clinically, but patients with symptoms suggestive of DVT were subjected to immediate phlebography. The phlebograms were performed according to a technique described earlier (Brodelius et al., 1971; Nylander, 1971). It can be summarized as follows. The lower leg was examined in a vertical position with horizontal beam direction. Contrast medium (30 ml Isopaque, Amin, Nyegaard) was injected into a dorsal foot vein. Frontal and lateral films were obtained. The deep veins of the knee, thigh and iliofemoral region were examined with the patient in the supine position and vertical beam direction. Another 30 ml of contrast medium were injected into the large saphenous vein at the level of the knee. The contrast medium was distributed to the deep veins through the perforating veins by two tourniquets, one firmly wrapped around the uppermost part of the thigh and the other around the leg below the knee. Frontal views of the iliofemoral veins were obtained before and after releasing the uppermost tourniquet. In a few patients, where the iliofemoral veins were occluded by thrombi, the iliac veins were visualized by injection of 20 ml of contrast medium into a superficial vein in the groin. Bilateral phlebograms were performed in 113 patients and 21 patients were subjected to unilateral phlebography. The results of the phlebograms were grouped according to the following system:

A. Normal.

B. Lower leg DVT (DVT confined to the veins of the lower leg and not extending above the popliteal vein).

C. Lower leg and femoral DVT (lower leg DVT with isolated thrombosis also in the deep veins of the thigh).

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D. Femoral DVT (isolated DVT in the thigh).

E. Extensive DVT (total occlusion of the deep veins in the lower limb up to the inguinal region).

The data were compared using the χ^2 test with Yates's correction and the Student's t test.

Results

The results of the phlebograms in all patients are presented in *Fig.* 1. Seventy-eight of the 134 patients included in the study had DVT (58 per cent). Fifty per cent of the thrombi engaged the thigh veins. Thrombi in the thigh without lower leg DVT were found in 10 patients (13 per cent). Most thrombi in the thigh region were isolated from thrombi in the calf (23 out of 39, 59 per cent). The distribution of DVT in relation to age, sex, type of hip prosthesis and side of operation is shown in *Table II.* The distribution of thrombi in bilateral phlebograms (*Fig.* 2) shows that lower leg DVT was as common in the operated leg as in the non-operated leg, whereas involvement of thigh veins was significantly more common in the operated leg ($P<0.05$). Patients with and without DVT, respectively, were compared with regard to age, time of operation, time of anaesthesia, operative haemorrhage, amount of homologous blood transfused and day of mobilization postoperatively. The results are shown in *Table III.* The patients with DVT were significantly older ($P<0.001$). There was no difference in the other variables between patients with and without DVT. Ten patients had DVT with symptoms—clinical DVT—and 2 more patients had clinical symptoms of DVT but the results of phlebography were normal. The patients with clinical DVT are indicated in *Fig.* 1 and *Table II.* All but one of the clinical thrombi occurred in the operated leg. Most clinical thrombi engaged the thigh and 60 per cent of these thrombi were extensive.

Discussion

The incidence of postoperative DVT, among other factors, depends on the diagnostic techniques used. In this study all deep veins, including the muscle veins of the calf, were included and the deep veins were examined up to the confluence with the inferior vena cava. All phlebograms were scrutinized by an experienced radiologist. All thrombi detected, no matter how small, were recorded as DVT. This might explain the high incidence of DVT in these patients despite dextran prophylaxis.

The high incidence of isolated thigh vein thrombi (29 per cent) in this study greatly exceeds the incidence of this type of thrombus in an unselected series of patients with acute leg thrombosis derived from the same urban population (Nylander and Olivecrona, 1976) and also the incidence reported after major general surgery (Bolton and Hoffman, 1975). This clearly indicates the increased risk for this type of thrombus in patients undergoing total hip replacement.

Lower leg thrombi occurred as often in the operated as in the non-operated leg, whereas thigh thrombi were significantly more frequent in the operated leg. This is in agreement with other studies (Hampson et al., 1974; Hume et al., 1976). In the autopsy study of Sevitt and Gallagher (1961) on patients with unilateral fractures of the lower limb, no relationship between thrombosis and the side of injury was established. However, deep vein thrombosis associated with major pulmonary embolism was more frequent in the injured limb in cases with unilateral thrombosis.

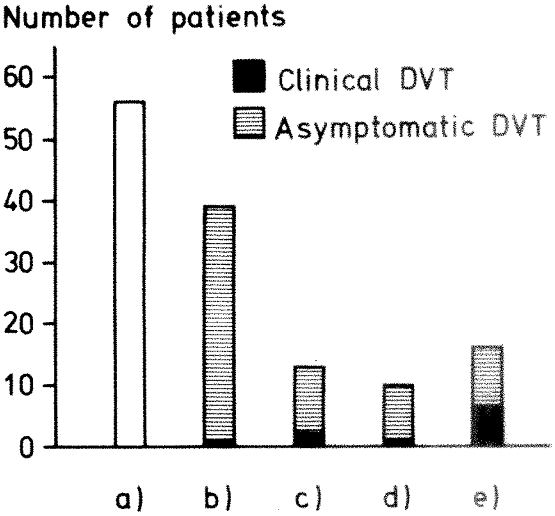

Fig. 1. Results of phlebograms: (a) normal; (b) lower leg DVT; (c) lower leg and femoral DVT; (d) isolated femoral DVT; (e) extensive DVT.

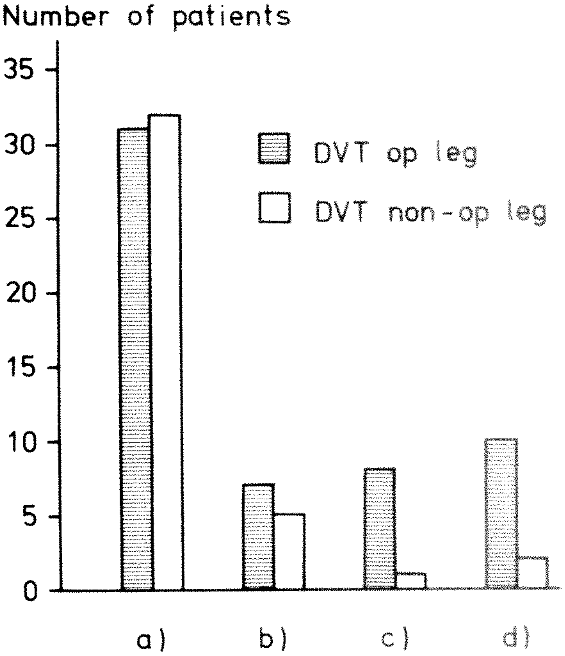

Fig. 2. Distribution of DVT in bilateral phlebograms: (a) lower leg DVT; (b) lower leg and femoral DVT; (c) isolated femoral DVT; (d) extensive DVT.

Clinical symptoms were more common in patients with thigh DVT. Even in extensive deep vein thrombosis, however, only one-third of the patients had clinical symptoms. The high percentage of asymptomatic thrombi in the thigh might explain why most fatal emboli after hip surgery occur without previous signs and symptoms of DVT (Johnson et al., 1976).

In the literature, opinions on the site of origin of venous thrombosis differ. Autopsy studies (McLaughlin and Paterson, 1951; Sevitt and

Table II: DISTRIBUTIONS OF THROMBI IN RELATION TO SEX, TYPE OF HIP PROSTHESIS AND SIDE OF OPERATION

	Sex		Hip prosthesis			Side of operation	
Phlebography	Male	Female	Charnley	Brunswick	Other	Right	Left
Lower leg DVT	14	25 (1)	14	23 (1)	2	18 (1)	15
Lower leg and femoral DVT	3	10 (1)	6 (1)	7		7	3 (1)
Isolated femoral DVT	3 (1)	7 (1)	5	5 (2)		4	6 (2)
Extensive DVT	7 (3)	9 (3)	8 (5)	8 (1)		7 (2)	8 (4)
All DVT	27 (54%)	51 (61%)	33 (61%)	43 (58%)	2	36 (48%)	32 (59%)
Normal	23 (46%)	33 (39%)	21 (39%)	31 (42%)	4	39 (52%)	22 (41%)
Total	50	84	54	74	6	75*	54

Figures in brackets indicate clinical thrombi.
* Five patients operated on the right side had no phlebograms of the operated limb.

Table III: COMPARISON OF PATIENTS WITH AND WITHOUT DVT

	DVT	Normal	Significance
Number	78	56	
Age (yr)	68 ± 7	63 ± 9	$P < 0{\cdot}001$
Day of mobilization	$2{\cdot}1 \pm 1{\cdot}4$	$2{\cdot}1 \pm 1{\cdot}7$	n.s.
Operation time (min)	111 ± 26	± 112 ± 29	n.s.
Duration of anaesthesia (min)	203 ± 39	215 ± 54	n.s.
Haemorrhage at operation (l)	$2{\cdot}213 \pm 0{\cdot}996$	$2{\cdot}071 \pm 970$	n.s.
Transfusion of homologous blood (l)	$1{\cdot}634 \pm 0{\cdot}852$	$1{\cdot}382 \pm 0{\cdot}891$	n.s.

Gallagher, 1961) establish that thrombi can start at multiple sites and that the iliofemoral region is as common as, and perhaps more important than, the calf as a site of DVT. Studies with the ^{125}I-fibrinogen uptake method and the Doppler ultrasound technique have shown that the majority of postoperative thrombi start in the calf veins and that femoral thrombi form by propagation from the calf (Kakkar et al., 1969; Bolton and Hoffman, 1975). The diverging results might be explained partly by technical difficulties in necropsy studies and by the insensitivity of the ^{125}I-fibrinogen method in diagnosing iliofemoral thrombi (Harris et al., 1975). An additional explanation is the time at which the investigations were performed. The ^{125}I-fibrinogen test has mainly been performed in the first 7–10 postoperative days while autopsy studies have been performed in a selected group of patients in the third week. The present study shows that the majority of femoral vein thrombi after total hip replacement are formed in the thigh. Since extensive thrombi in the leg showed the same distribution as isolated femoral thrombi (with the majority being formed in the operated leg), it might be asked whether these thrombi are formed by propagation peripherally from an isolated thrombus in the thigh. In favour of this view are the observations by Hume et al. (1976) that thrombi detected late postoperatively were more extensive. As the patients were monitored by the ^{125}I-fibrinogen method these thrombi would have been detected earlier if they had started in the calf. Thrombi originating from the large veins of the thigh might exist for a long time before occluding the vein completely and causing clinical symptoms. This agrees with the observation that clinical DVT after total hip replacement is often diagnosed 2–3 weeks after operation (Charnley, 1972).

Acknowledgements

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References

AHLBERG Å., NILLIUS A., ROSBERG B. et al. (1977) Preoperative normovolemic hemodilution in total hip arthroplasty. A clinical study. *Acta Chir. Scand.* **143**, 407–411.

BOLTON J. P. and HOFFMAN V. J. (1975) Incidence of early post-operative iliofemoral thrombosis. *Br. Med. J.* **1**, 247–249.

BRODELIUS Å., LÖRINC P. and NYLANDER G. (1971) Phlebographic technique in the diagnosis of acute deep venous thrombosis in the lower limb. *Am. J. Roentgenol.* **111**, 794–801.

CHARNLEY J. (1972) Prophylaxis of postoperative thromboembolism. *Lancet* **2**, 134–135.

EVARTS M. and FEIL J. (1971) Prevention of thromboembolic disease after elective surgery of the hip. *J. Bone Joint Surg.* **53A**, 1271–1280.

HAMPSON W. G. J., HARRIS F. C., LUCAS H. K. et al. (1974) Failure of low-dose heparin to prevent deep vein thrombosis after hip replacement arthroplasty. *Lancet* **2**, 795–797.

HARRIS W. H., SALZMAN E. W., ATHANASOULIS C. et al. (1975) Comparison of ^{125}I-fibrinogen count scanning with phlebography for detection of venous thrombi after elective hip surgery. *N. Engl. J. Med.* **292**, 665–667.

HARRIS W. H., SALZMAN E. W., ATHANASOULIS C. A. et al. (1977) Aspirin prophylaxis of venous thromboembolism after total hip replacement. *N. Engl. J. Med.* **297**, 1246–1249.

HUME M., TURNER R. H., KURAKIOSE T. X. et al. (1976) Venous thrombosis after total hip replacement. *J. Bone Joint Surg.* **58A**, 933–938.

JOHNSON R., GREEN J. H. and CHARNLEY J. (1976) Pulmonary embolism following the Charnley total hip replacement and its prophylaxis. Centre for Hip Surgery, Wrightington Hospital, internal publication No. 64.

KAKKAR V. V., HOWE C. T., FLANC C. et al. (1969) Natural history of postoperative deep vein thrombosis. *Lancet* **2**, 230–232.

MCLAUGHLIN J. and PATERSON J. C. (1951) Some basic observations on venous thrombosis and pulmonary embolism. *Surg. Gynecol. Obstet*, **93**, 1–8.

NYLANDER G. (1971) Phlebographic diagnosis of acute deep leg thrombosis: venography. In: ABRAMS H. L. (ed.) *Angiography*, 2nd ed. Boston, Little Brown, pp. 1251–1271.

NYLANDER G. and OLIVECRONA H. (1976) The phlebographic pattern of acute leg thrombosis within a defined urban population. *Acta Chir. Scand.* **142**, 505–511.

SEVITT S. and GALLAGHER N. (1961) Venous thrombosis and pulmonary embolism. A clinicopathological study in injured and burned patients. *Br. J. Surg.* **48**, 475–489.

STAMATAKIS J. B., SAGAR S., MAFFEI F. H. et al. (1976) Femoral vein thrombosis and total hip replacement arthroplasty. *Br. J. Surg.* **63**, 668–669.

WALSH P. N., ROGERS P. H., MARDER V. J. et al. (1976) The relationship of platelet coagulant activities to venous thrombosis following hip surgery. *Br. J. Haematol.* **32**, 421–437.

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Ambulatory calf volume plethysmography in the assessment of venous insufficiency*

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SUMMARY

Ambulatory calf volume plethysmography has been used to study venous insufficiency in 50 lower limbs. The results demonstrate that it is possible to determine the presence of venous insufficiency and differentiate between normal limbs, limbs with superficial venous insufficiency only, limbs with deep venous insufficiency and limbs with deep venous insufficiency and occlusion by determining the ambulatory volume change and maximum venous outflow or venous volume.

VENOUS insufficiency can be assessed objectively by the measurement of ambulatory venous pressure (Pollack et al., 1949; De Camp et al., 1951; Lewis et al., 1973; Kriessman, 1974). However, this is an invasive technique not suitable for the routine screening of a large number of patients. In the past, venous occlusion plethysmography has been used mainly to establish the patency of deep veins (Dahn and Erikson, 1968; Hallbook and Gothlin, 1971) or to determine the competence of deep venous valves (Bygdeman et al., 1971; Barnes et al., 1972). Recently, it has been suggested that the procedure may be used in the diagnosis of valvular incompetence of both superficial and deep veins (Barnes et al., 1975; Holm, 1976), or to identify in patients with varicose veins segments of normal superficial veins to be preserved during surgical treatment (Holm et al., 1974).

The purpose of the present study was to determine whether ambulatory calf volume plethysmography, which is non-invasive, could distinguish between normal limbs, limbs with superficial valvular incompetence only, limbs with deep valvular incompetence and limbs with deep valvular incompetence and occlusion. In addition, we wanted to develop a test that was not only qualitative but would provide a quantitative measure of the severity of venous incompetence as determined by venous pressure. A non-invasive test that has achieved this had not previously been reported.

Patients and methods

Doppler ultrasound

Directional Doppler ultrasound (Parks, Model 806) was used to determine the presence of reflux at the saphenofemoral and saphenopopliteal junctions and in the popliteal vein. The patients were examined standing. The probe was positioned over the femoral vein at the groin. This position was determined by first localizing the femoral artery and then moving the probe medially until the typical venous flow was heard on manual compression of the thigh. The probe was adjusted so that the maximum audible signal was obtained. The changes on respiration, on Valsalva manoeuvre and on manual calf compression and release were noted. Reflux at the saphenofemoral junction was diagnosed if there was retrograde flow during the Valsalva manoeuvre and on release of calf compression, provided this reflux was abolished by compression of the long saphenous vein at mid-thigh level. The probe was then placed behind the knee, which was slightly flexed, while the patient's weight was on the opposite limb. The position of the probe was adjusted so that the signal from the popliteal artery was audible in addition to the signal from the popliteal vein on calf compression. On release of calf compression, the presence of retrograde flow which was not abolished by digital compression of the short saphenous vein, indicated incompetence of the popliteal valves. Retrograde flow on calf release which was abolished by digital compression of the short saphenous vein indicated reflux at the saphenopopliteal junction.

Ambulatory venous pressure

The ambulatory venous pressure was determined in all limbs. A 21G (bore 20G) 'butterfly' needle was inserted into a vein on the dorsum of the foot and was connected through an Akers transducer (model 840) and a BAP 001 amplifier to a potentiometric pen recorder (J. and J. Instruments, model CR 55amK2).

Venous pressure was measured with the patient standing still and then doing a tip-toe exercise for 20 s at a rate of one heel raising movement per second. This was repeated once after inflating a 2·5-cm pneumatic cuff at the ankle to a pressure of 140 mmHg and a second time after inflating a 2·5-cm pneumatic cuff at the thigh to a pressure of 180 mmHg. Venographic studies have demonstrated that the above pressures will allow occlusion of the superficial veins only, because of the small width of these cuffs (Nicolaides et al., 1971).

Ascending venography

Ascending venography was done in all limbs, except in the 15 normal limbs, in order to determine the presence or absence of deep venous occlusion (Craig, 1977).

Ambulatory calf volume plethysmography

Ambulatory calf volume plethysmography was done in all limbs, using a mercury-in-Silastic strain-gauge plethysmograph (Whitney, 1953) (Model EC-2 supplied by D. E. Hokanson) connected to a pen recorder (Mingograf 34). Two channels were used so that both limbs could be studied simultaneously. The strain-gauge was placed around the thickest part of the calf. The maximum venous outflow (MVO) was first determined with the patient supine and the legs elevated 10° to the horizontal by applying conical cuffs 25 cm wide to the thighs inflated at 60 mmHg for 2 min and then suddenly released. The venous volume (VV), which is the maximum increase in the calf volume, and the maximum venous outflow were calculated from the recordings of the calf volume during the period of occlusion and from the slope of the emptying curve during the first second after release of the thigh cuff (*Fig. 1a*). The coefficient of variation of the determinations of the MVO and VV was less than 6 per cent; this was obtained by repeated measurements in 6 limbs of 3 normal volunteers on 5 consecutive days. The MVO was expressed in ml per 100 ml of tissue per minute (Hallbook and Gothlin, 1971) and the VV in ml per 100 ml of tissue (Dahn and Erikson, 1968). Subsequently, the patient was asked to stand and repeatedly to raise himself on his toes (tip-toeing) at the rate of one movement per second for a period of 20 s. The ambulatory volume change (AVC), which was the maximum volume change during exercise, and the refilling time (t) (Holm, 1976) after exercise were obtained (*Fig. 1b*). The AVC was expressed in ml per 100 ml of tissue and t in seconds. The exercise was repeated with a cuff 2·5 cm wide just below the knee at 100 mmHg, which occluded the superficial veins.

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* Based on a paper presented at a meeting of the Surgical Research Society of Great Britain and Ireland in Manchester, July 1977.

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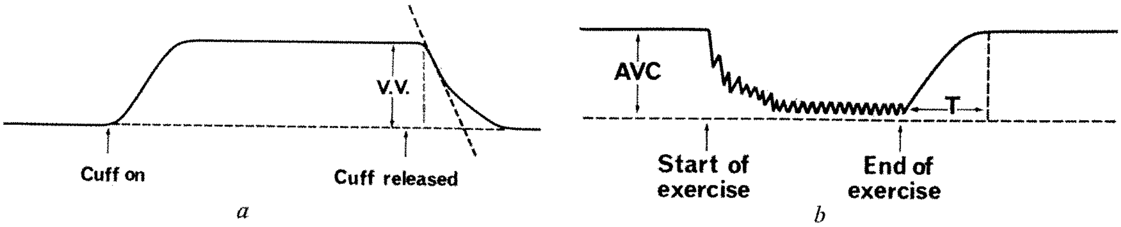


Fig. 1. *a*, Recording of the change in calf volume (VV = venous volume) during venous occlusion (2 min) and after sudden release of the cuff with the leg elevated 10°. (Initial slope = maximum venous outflow in ml per 100 ml per minute.) *b*, Recording of the change in calf volume (AVC = ambulatory volume change) before, during and immediately after the end of tip-toeing (exercise period was 30 s). (T = refilling time in seconds.)

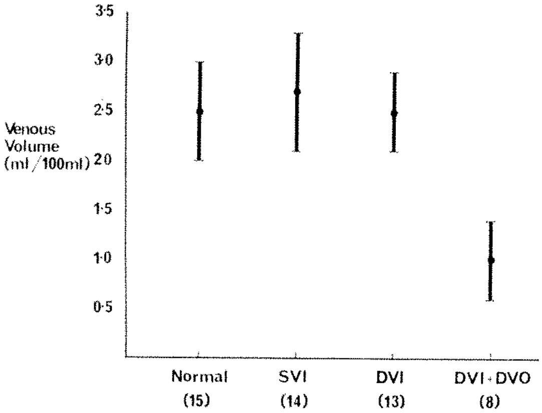


Fig. 2. Results of venous volume. (Values are mean ±s.d.)

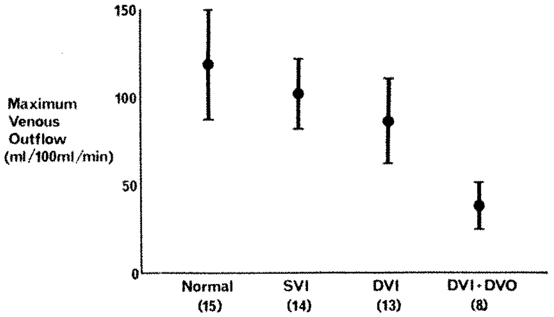


Fig. 3. Results of maximum venous outflow. (Values are mean±s.d.)

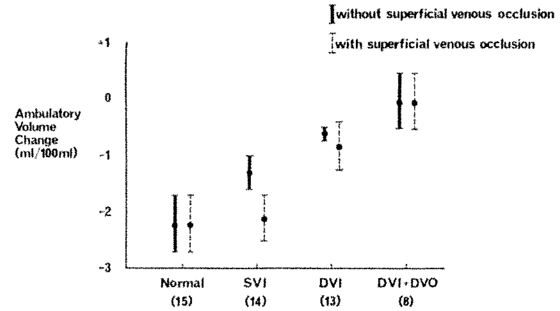


Fig. 4. Results of ambulatory volume change with and without occlusion of the superficial veins. (Values are mean±s.d.)

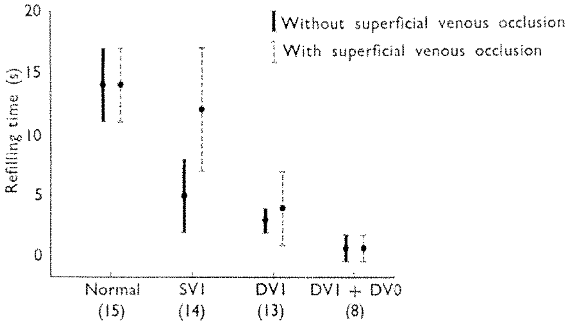


Fig. 5. Results of refilling time with and without occlusion of the superficial veins. (Values are mean±s.d.)

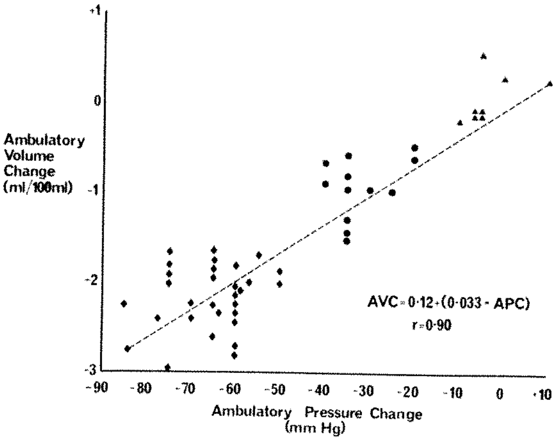


Fig. 6. Regression line between ambulatory volume change (AVC) and ambulatory pressure change (APC). ◆, Limbs with normal deep venous system; ●, limbs with DVI and without DVO; ▲, limbs with DVI and DVO.

Patients

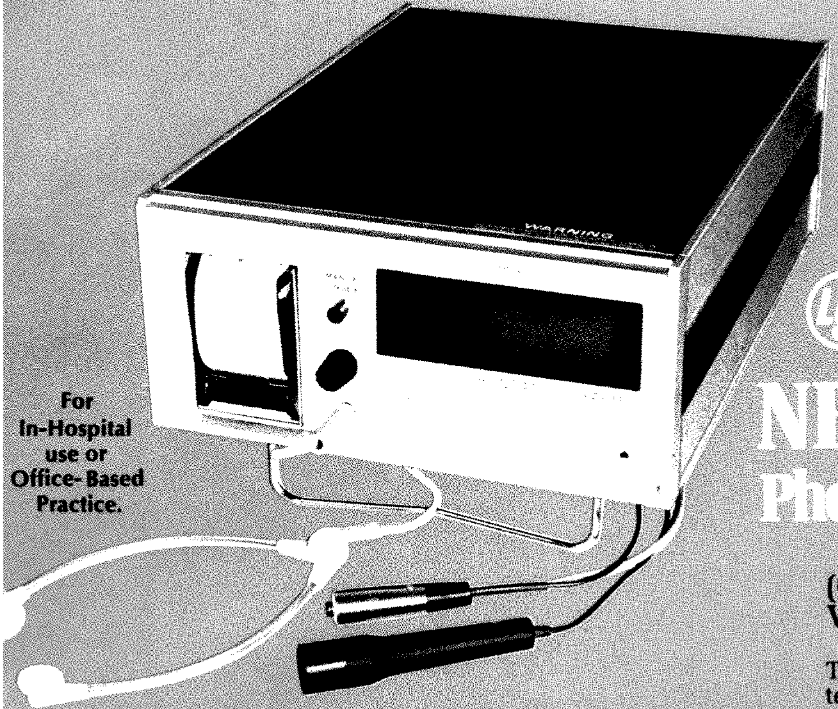
Fifty limbs of 27 subjects (11 male and 16 female) have been studied. The limbs were classified into the following four groups according to the criteria stated below.

Normal: Fifteen limbs were classified as normal because Doppler ultrasound did not demonstrate any reflux and the ambulatory venous pressure was less than 35 mmHg.

Superficial venous incompetence with competent valves in the deep veins (SVI): Fourteen limbs were included in this group because Doppler ultrasound demonstrated reflux at the saphenofemoral or saphenopopliteal junctions, but no popliteal reflux. The ambulatory venous pressure became less than 33 mmHg only by applying the venous cuffs during tip-toeing.

NEW Recording Phonoangiograph

(CPA) for Cerebral Vascular evaluation



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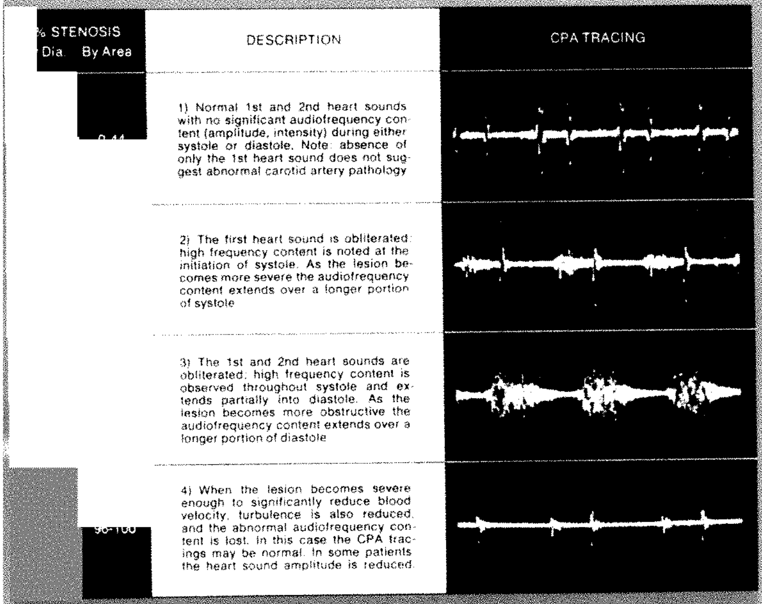
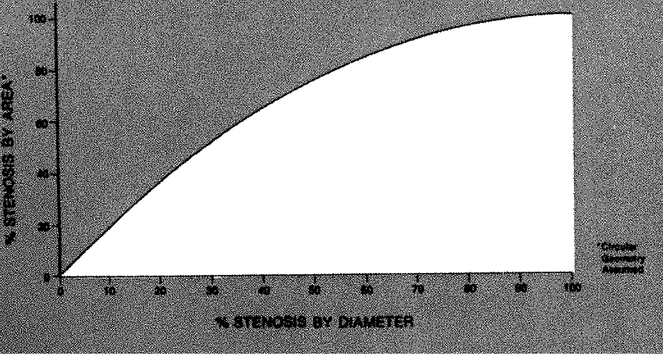
Practice.



% STENOSIS Dia.	By Area	DESCRIPTION	CPA TRACING
		1) Normal 1st and 2nd heart sounds with no significant audiofrequency content (amplitude, intensity) during either systole or diastole. Note: absence of only the 1st heart sound does not suggest abnormal carotid artery pathology	
		2) The first heart sound is obliterated: high frequency content is noted at the initiation of systole. As the lesion becomes more severe the audiofrequency content extends over a longer portion of systole	
		3) The 1st and 2nd heart sounds are obliterated: high frequency content is observed throughout systole and extends partially into diastole. As the lesion becomes more obstructive the audiofrequency content extends over a longer portion of diastole	
		4) When the lesion becomes severe enough to significantly reduce blood velocity, turbulence is also reduced, and the abnormal audiofrequency content is lost. In this case the CPA tracings may be normal. In some patients the heart sound amplitude is reduced.	



The major diagnostic CPA parameters are absence or presence of 1st and 2nd heart sounds, absence or presence of high-frequency content in systole or systole and diastole, and the differential character of the three traces taken on each side.

The sensitivity, amplification, quantitation, and frequency range of CPA is well above the capacity of the human ear. This allows appreciation of bruits that cannot be heard with a stethoscope. The advantages of quantitation and hard copy are obvious.

CPA is helpful even for the experienced examiner in identifying transmitted murmurs.

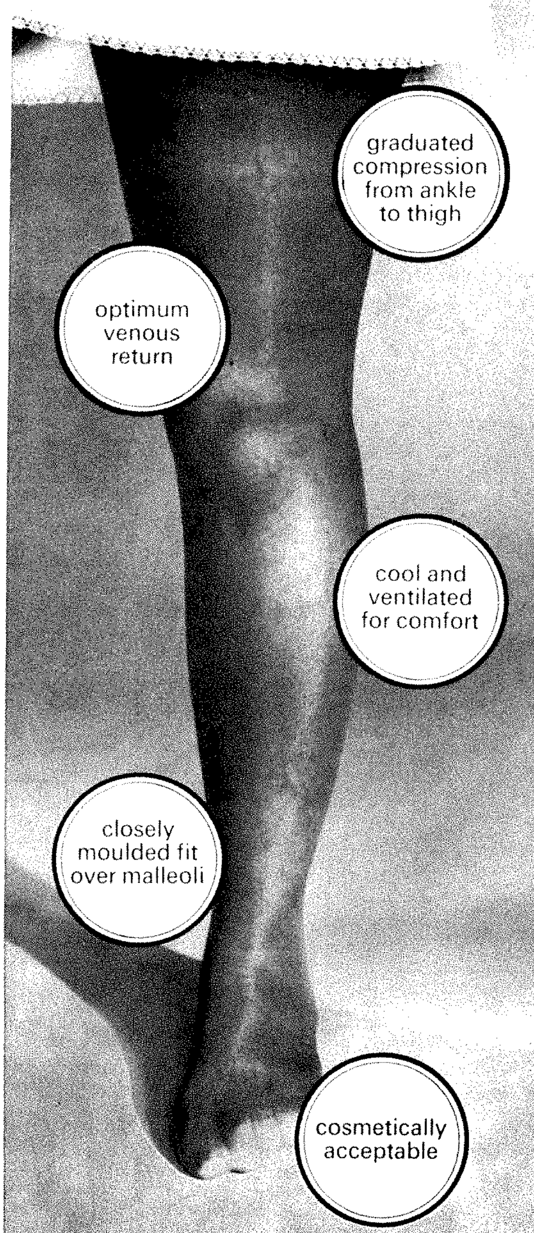
Patient groups most often suggested for routine Cerebral Vascular Evaluation include:

a) Hospital admissions over 60 years of age.
b) Patients undergoing cardiopulmonary bypass.
c) Patients with multiple risk factors for arteriosclerotic disease.

References, bibliography and details on request.

Life Sciences Inc.
270 Greenwich Avenue
Greenwich, Connecticut 06830 U.S.A.
Tel. 203 869-2011

Varicose veins?


graduated compression from ankle to thigh
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cool and ventilated for comfort
closely moulded fit over malleoli
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Deep venous incompetence (*DVI*): Thirteen limbs were included in this group because Doppler ultrasound demonstrated popliteal reflux. The ambulatory venous pressure was high (>45 mmHg) and was not affected by the venous cuffs. Superficial venous incompetence was also present in the majority of these patients.

Deep venous incompetence and occlusion (*DVI+DVO*): Eight limbs were included in this group because venography demonstrated occlusion of the iliofemoral segment and the ambulatory venous pressure was greater than 70 mmHg even when the venous cuffs were inflated.

Results

There was no significant difference in the mean venous volume of normal limbs, limbs with superficial venous incompetence and limbs with deep venous incompetence without occlusion. However, the mean venous volume of the limbs with deep venous occlusion was significantly lower and there was no overlap between this and the other groups (*Fig*. 2). The venous volume was always less than 1·5 ml/100 ml in the presence of deep venous occlusion and always higher than 2·0 ml/100 ml in the absence of occlusion.

The maximum venous outflow was always less than 55 ml 100 ml^{-1} min^{-1} in the presence of deep venous occlusion and more than 65 ml 100 ml^{-1} min^{-1} in the absence of occlusion. There was considerable overlap of the values of maximum venous outflow in the remaining three groups (*Fig*. 3).

The results of the ambulatory volume change are shown in *Fig*. 4. The mean ambulatory volume change was −2·20 (s.d. ± 0·5) in normal limbs. (The negative sign indicates that the calf volume is decreased.) The mean ambulatory volume change was −1·3 (s.d. ± 0·3) in limbs with superficial venous incompetence, −0·60 (s.d. ± 0·1) in limbs with deep venous incompetence and −0·06 (s.d. ± 0·5) in limbs with deep venous incompetence and occlusion. In the last group (DVI+DVO) the ambulatory volume change was negative and small (−0·25 ml/100 ml) in 6 limbs and positive (+0·40 ml/100 ml) (i.e. *calf volume increased*) in 2 limbs which belonged to patients with pain on walking. The ambulatory volume change was not affected by superficial venous occlusion in normal limbs and limbs with deep venous incompetence with or without occlusion, but it was brought into the normal range in the limbs with superficial incompetence only. Thus, the only overlap was between the group with deep venous incompetence and the group with deep venous incompetence and occlusion (*Fig*. 4).

The results of the refilling time studies are shown in *Fig*. 5. The refilling time did not demonstrate the same degree of separation between the groups as the ambulatory volume change because of considerable overlap.

There was a linear relationship between the ambulatory venous change and the ambulatory pressure change. The regression line and equation are shown in *Fig*. 6, in which the limbs with deep venous occlusion, limbs with deep venous incompetence and limbs with a normal deep venous system (ambulatory venous pressure and calf volume change measured with venous cuffs occluding the superficial veins) are shown as three completely separate groups.

Discussion

The maximum venous outflow reflects the functional capacity of the venous system to drain the blood collected in the lower limb during the period of venous occlusion. The venous volume is a measure of the venous capacity of the limb; its value reflects the space available for blood to accumulate. Both provide complete separation between limbs with and without deep venous occlusion and are of diagnostic value (*Figs*. 2, 3).

The ambulatory volume change without and with superficial venous occlusion provides information about the efficacy of the calf muscle pump, which depends on the state of the deep venous valves and on the patency of the deep venous system. In the limbs with superficial incompetence, when the superficial reflux was abolished and the efficacy of the calf muscle pump was restored by a below-knee cuff, the ambulatory volume change became normal. However, if deep reflux was present, even with associated superficial venous reflux, the value of the ambulatory volume change did not alter significantly after application of the venous cuffs. Thus, it was possible to achieve complete separation of normal limbs, limbs with superficial venous incompetence and limbs with deep venous incompetence.

The linear relationship (*Fig*. 6) between ambulatory volume change and ambulatory pressure change suggests that changes in calf volume vary according to changes in pressure. It also supports the validity of this non-invasive test.

By measuring the ambulatory volume change and either the maximum venous outflow or venous volume it is possible to produce complete separation of all four groups; i.e. it is possible to differentiate between normal limbs, limbs with superficial venous incompetence only, deep venous incompetence and deep venous incompetence with occlusion.

This is a useful screening test for limbs with suspected venous incompetence and is an aid in providing an accurate diagnosis without recourse to invasive tests. In addition, it provides a quantitative estimation of the degree of venous insufficiency. Possible future applications of this non-invasive method are the study of the natural history of deep venous thrombosis and post-phlebitic limb, the effect of elastic stockings, surgical treatment and sclerotherapy. It may also provide a better selection of patients with deep venous occlusion for reconstructive surgery.

Recent work on foot volume changes (Norgren, 1975; Annotation, 1978) during exercise suggests that useful information which correlates with the degree of venous insufficiency can be obtained. However, the results of foot volumetry show considerable overlap and cannot produce a complete separation of the various groups as achieved by calf volume plethysmography. In addition, foot volumetry does not provide a quantitative measure of the venous outflow. Foot volumetry will probably prove to be a simple screening test to identify limbs with venous insufficiency. Calf volume plethysmography is not only a screening test but also a test that can provide a precise diagnosis.

Acknowledgements

We are grateful to Professor H. Dudley and Mr John Hobbs for their encouragement and support, and for allowing us to study their patients; to the Gulbenkian Foundation for providing a grant to J. F. e F., to Scholl (USA) for a research fellowship to J. H. and to Dr D. Sutton for allowing us to use the facilities of the X-ray Department.

References

ANNOTATION (1978) Foot volumetry in venous insufficiency. *Lancet* **1**, 315.

BARNES R. W., COLLICOTT P. E. et al. (1972) Non-invasive quantitation of maximum venous outflow in acute thrombophlebitis. *Surgery* **72**, 971–979.

BARNES R. W., ROSS E. A. and STRANDNESS E. (1975) Differentiation of primary from secondary varicose veins by Doppler ultrasound and strain-gauge plethysmography. *Surg. Gynecol. Obstet.* **141**, 207–211.

BYGDEMAN S., ASCHBERG S. and HINDMARSH T. (1971) Venous plethysmography in the diagnosis of chronic venous insufficiency. *Acta Chir. Scand.* **137**, 423–428.

CRAIG J. O. N. C. (1977) Investigation of the leg veins by venography. In: HOBBS J. T. (ed.) *Treatment of Venous Disorders.* Lancaster, Medical & Technical Publishing, pp. 83–95.

DE CAMP P. T., SCHRAMEL R. J., RAY C. J. et al. (1951) Ambulatory venous pressure determinations in post-phlebitic and related syndromes. *Surgery* **29**, 44–52.

DAHN I. and ERIKSON F. (1968) Plethysmographic diagnosis of deep venous thrombosis. *Acta Chir. Scand.* Suppl. 398, pp. 33–42.

HALLBOOK T. and GOTHLIN J. (1971) Strain-gauge plethysmography and phlebography in diagnosis of deep venous thrombosis. *Acta Chir. Scand.* **137**, 37–53.

HOLM J. S. E. (1976) A simple plethysmographic method for differentiating primary from secondary varicose veins. *Surg. Gynecol. Obstet.* **143**, 609–612.

HOLM J., NILSSON N. J., SCHERSTEN T. et al. (1974) Elective surgery for varicose veins. A simple method for evaluation of the patients. *J. Cardiovasc. Surg.* **15**, 565–572.

KRIESSMAN A. (1974) Peripheral phlebodynamometry. Quantitative method for the differentiation of venous insufficiency in the lower limbs. *Dtsch. Med. Wochenschr.* **99**, 1025–1026.

LEWIS J. D., PARSONS D. C. S., NEEDHAM T. et al. (1973) The use of venous pressure measurements and directional Doppler recordings in distinguishing between superficial and deep valvular incompetence in patients with deep venous insufficiency. *Br. J. Surg.* **60**, 312.

NICOLAIDES A. N., KAKKAR V. V., FIELD E. S. et al. (1971) The origin of deep vein thrombosis: a venographic study. *Br. J. Radiol.* **44**, 653–663.

NORGREN L. (1975) Foot-volumetry before and after surgical treatment of patients with varicose veins. *Acta Chir. Scand.* **141**, 129–134.

POLLACK A. A., TAYLOR B. E., MYERS T. T. et al. (1949) Venous pressure in the saphenous vein at the ankle in man during exercise and changes in posture. *J. Appl. Physiol.* **1**, 649–662.

WHITNEY R. J. (1953) Measurement of volume changes in human limbs. *J. Physiol.* (*Lond.*) **121**, 1–27.

Paper accepted 24 November 1978.

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Axillary vein entrapment

A. H. BOONTJE*

SUMMARY

This paper describes a patient with right axillary vein obstruction resulting from compression of the vein due to anomalous muscle tissue extending from the latissimus dorsi muscle across the neurovascular bundle to the pectoralis major muscle. This 'axillopectoral muscle' causing entrapment of the axillary vein has been described in only a few cases. These previous reports are discussed, with special reference to the symptoms and phlebographic findings. The obstruction and the symptoms caused by it are intermittent; the phlebographic features are characteristic.

THE causes of venous obstruction in the upper limb have been divided into two groups. There may be primary effort thrombosis or secondary obstruction of the axillary or subclavian vein due to a trauma, compression caused by malignant processes or venous catheters. The obstruction described as primary, however, often proves to be secondary. In many of these cases there is a costoclavicular compression syndrome, but only rarely is there external compression, which is caused by various anomalies (Campbell et al., 1977). One such is a muscular anomaly consisting of muscle fibres extending from the latissimus dorsi muscle to the pectoralis major muscle. The following case report describes a patient with this rare condition, diagnosed preoperatively.

Case report

A woman aged 37 was referred to our university hospital with an 18-month history of heaviness and stiffness in the right arm of gradual onset. The patient found it virtually impossible to pursue her regular organ playing. The hand was usually somewhat swollen, especially at rest, and sometimes slightly discoloured. The patient slept poorly because of the disagreeable sensations, which persisted overnight. There had been no trauma to the arm.

Examination revealed that the right hand was slightly swollen. There was no discoloration. The venous patterns of the arms were symmetrical. No distended veins were visible on the right shoulder. The arterial circulation was normal. No bruits were audible in the neck. There were no clinical abnormalities in the arm nor in the axillary region.

General physical examination disclosed nothing unusual. There were no neurological abnormalities. The various pertinent studies with the arm in several different positions were all negative.

Phlebography of the right arm was then carried out (*Fig.* 1). This revealed a severe obstruction of the right axillary vein. A non-recanalized thrombosis seemed unlikely. Such a thrombosis as a rule results from costoclavicular compression and the venous obstruction was localized too distally. The next possible cause considered was compression of the axillary vein as a result of an aberrant muscle (Corning, 1949). Consequently, we decided upon surgical exploration.

The right axilla was opened by a longitudinal incision in the proximal part of the medial bicipital sulcus extending to the chest wall, curving along the edge of the pectoralis major muscle. The axillary vein was exposed. The calibre of this vein was normal from its distal part to just past the lower edge of the greater pectoral muscle, where a 1-cm hour-glass shaped stenosis was seen (*Fig.* 2). There was no thrombus. The venous wall was not thickened at the site of the stenosis. A taut band was present 0·5 cm cranial to the stenosis (*Fig.* 2). As the abducted arm was elevated, this taut band compressed the axillary vein precisely at the level of the stenosis. This band seemed to be the muscular anomaly mentioned above, and it ran from the latissimus dorsi muscle to the pectoralis major muscle.

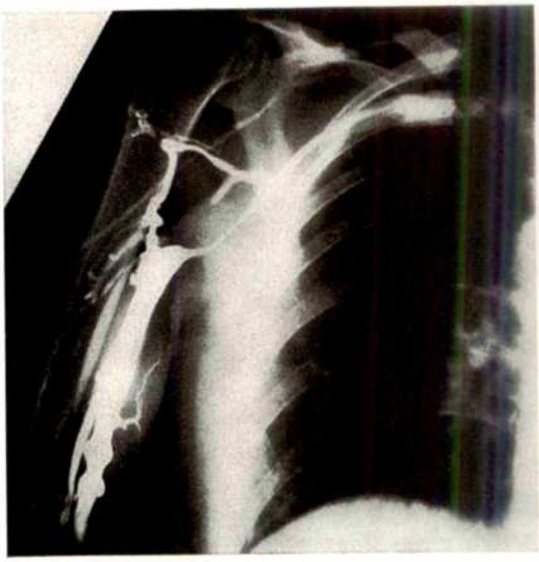

Fig. 1. Phlebography of the right arm. Almost complete occlusion of the axillary vein.

The band was resected. After some delay, the stenosed part of the axillary vein spontaneously resumed an acceptable calibre (*Fig.* 3). Patch angioplasty seemed unnecessary and the wound was closed in layers.

Microscopic examination of the resected specimen revealed striated muscle, thus confirming the diagnosis of a muscular anomaly.

The postoperative course was uneventful. Follow-up phlebography 2 weeks later revealed only a slight stricture of the axillary vein. The patient resumed her normal household duties, her complaints gradually disappeared and she was able to play the organ again.

Follow-up phlebography 6 months after the operation revealed excellent patency of the axillary vein without any constriction (*Fig.* 4), and the right hand no longer showed any signs of venous congestion.

Discussion

The symptoms and signs of obstruction of the axillary or subclavian vein are well known and consist of pain and tiredness in the arm, swelling, discoloration and an intensified venous pattern. This symptomatology is not specific for any particular cause of obstruction.

Phlebography may be required in axillary vein obstruction when no externally obvious cause is present. In some cases the site of venous obstruction is not at the level of the thoracic outlet, but more distal. Obstruction of the axillary vein caused by a muscular anomaly gives typical phlebographic features. The phlebogram of our patient (*Fig.* 1) is identical to that reproduced by Dodd and Cockett (1976). At the level of the lower axillary border the axillary vein shows a typically tapered stenosis, beyond which it gradually resumes its normal calibre. Two different muscular abnormalities can be distinguished. In most cases an aberrant muscle extends

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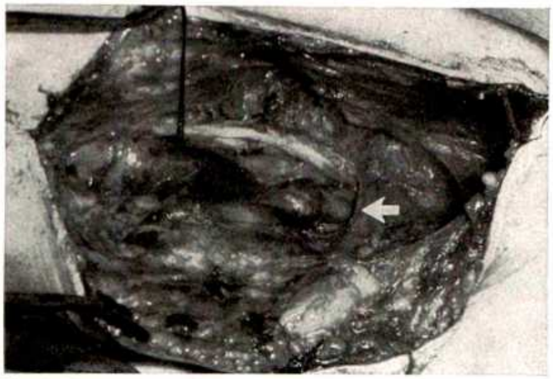


Fig. 2. Entrapment of the axillary vein by a muscular band (arrow).

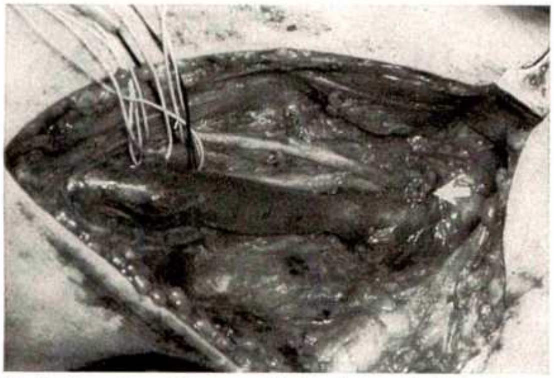


Fig. 3. Resection of the muscular band (arrow). Dilatation of the axillary vein is visible.

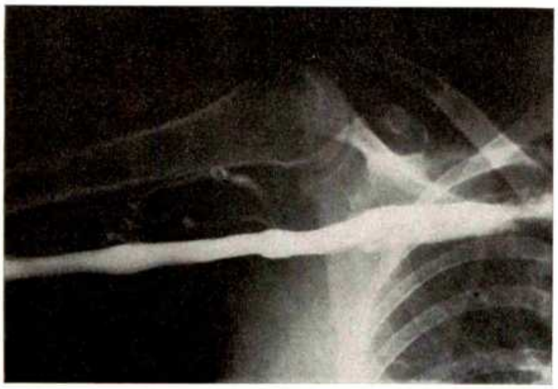


Fig. 4. Phlebography of the right arm 6 months after operation. The axillary vein is of normal calibre.

from the latissimus dorsi muscle to the pectoralis major muscle and lies across the neurovascular bundle. This is known as *Langer'ser Armbogen* in German (Corning, 1949)—'Langer's arm arch' in English or the axillopectoral muscle (*Fig*. 5).

Rarely, aberrant muscle tissue extends from the latissimus dorsi muscle to the coracoid process—*Langer'ser Achselbogen* in German—'Langer's axillary arch'. Long-standing intermittent compression of the vein caused by this anomaly and dependent on the position of the arm can lead to venous thrombosis.

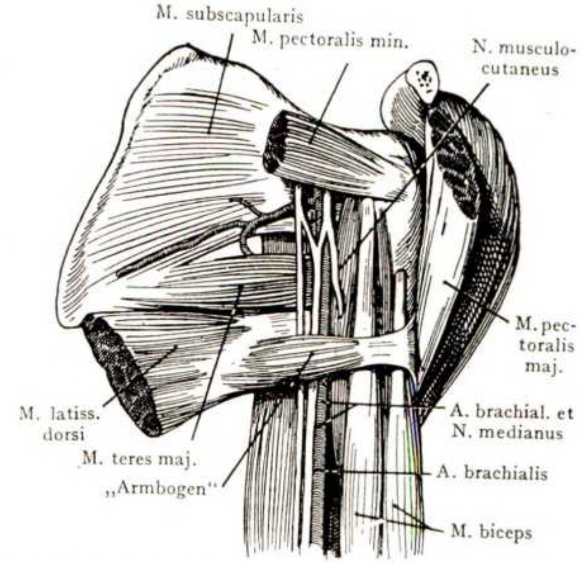


Fig. 5. Anatomy of the axilla with the axillopectoral muscle. (*From* Corning, 1949.)

It is likely that this anomaly is not as rare as it appears to be, but it is generally not diagnosed and explored. Apart from the case described by Dodd and Cockett (1976), Tilney et al. (1970) briefly mention a patient with this anomaly in a review article on venous thrombosis of the upper limb. Sachatello (1977) described a 15-year-old girl with intermittent swelling and discoloration of the hand caused by an axillopectoral muscle. Visible fullness in the axillary region was noticed in this patient. Both Tilney's and Sachatello's patient had a venous obstruction without thrombosis, and in both cases the aberrant muscle was resected.

Saitta and Baum (1962) described a boy aged 10 with a visible and palpable mass in the right axillary region, particularly during abduction of the arm. There was no evidence of venous obstruction. Exploration revealed that the mass was a muscular anomaly, which was resected.

Treatment of this problem is simple: after axillary exploration the aberrant muscle should be resected, thus abolishing the compression. Venous reconstruction can then be considered if a thrombus is present or if the venous wall is damaged.

References

CAMPBELL C. B., CHANDLER J. G., TEGTMEYER C. J. et al. (1977) Axillary, subclavian and brachiocephalic vein obstruction. *Surgery* **82**, 816–826.

CORNING H. K. (1949) *Lehrbuch der topographischen Anatomie*, 24th ed. Munich, Bergmann, p. 635.

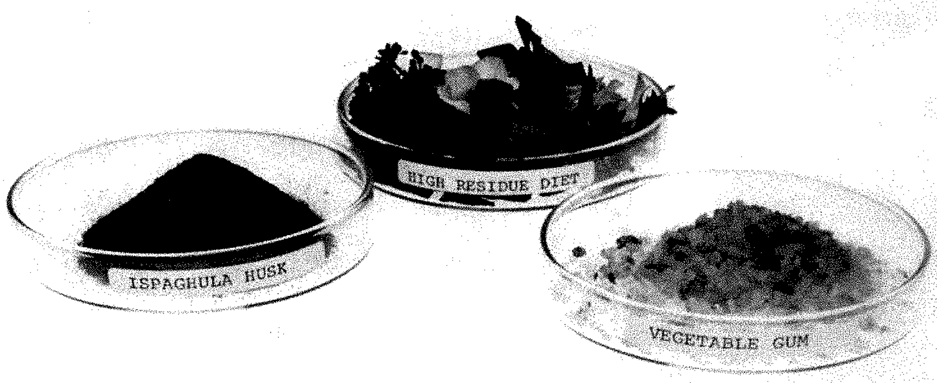
DODD H. and COCKETT F. B. (1976) *The Pathology and Surgery of the Veins of the Lower Limb*, 2nd ed. Edinburgh, Churchill Livingstone, pp. 206–207.

SACHATELLO C. R. (1977) The axillopectoral muscle (Langer's axillary arch): a cause of axillary vein obstruction. *Surgery* **81**, 610–612.

SAITTA G. F. and BAUM V. (1962) Langer's axillary arch. *JAMA* **180**, 122.

TILNEY N. L., GRIFFITHS H. J. G. and EDWARDS E. A. (1970) Natural history of major venous thrombosis of the upper extremity. *Arch. Surg.* **101**, 792–796.

Paper accepted 6 November 1978.



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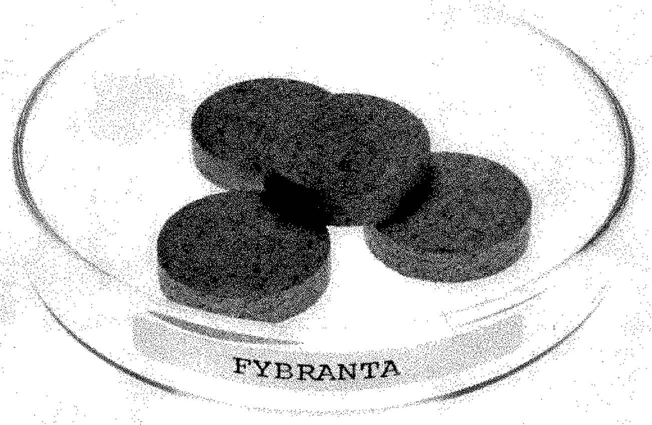

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Br. J. Surg. Vol. 66 (1979) 333–337

Partial and complete atrophy affecting hepatic segments and lobes

J. M. HAM*

SUMMARY
Thirty-four patients with atrophic lesions of liver segments or lobes are described. The primary diagnoses included alcoholic liver disease, various forms of cirrhosis, hydatid disease, tumours and sclerosing cholangitis. Seventeen patients had complete atrophy of the segment or lobe and the other 17 patients had partial atrophy (i.e. a reduction of at least 50 per cent in the size of the affected area). Complete atrophy affected the left lobe more frequently than the right. The condition is important, first, because it is more common than is generally recognized, and second, because it may create considerable diagnostic and therapeutic problems.

ATROPHIC lesions of the liver are usually regarded as pathological curiosities of little or no clinical importance (Benz et al., 1952; Bockus, 1965). However, these lesions have been seen quite frequently in this unit and in some patients they have created considerable diagnostic and therapeutic problems.

This report is concerned with 34 patients, 17 of whom had complete atrophy of a liver segment or lobe and 17, partial atrophy. There was a variety of primary diagnoses; these illustrate the fact that liver atrophy may be due to vascular or biliary obstruction, to direct hepatic cell injury or to combinations of these factors.

Definitions

Complete atrophy was diagnosed if the affected part of the liver was markedly shrunken and little or no normal liver tissue remained. Partial atrophy was defined as a reduction of at least 50 per cent in the size of a recognized anatomical segment or lobe. Patients with patchy areas of scarring and atrophy, such as are commonly seen in the various types of macronodular cirrhosis, were not included in the study.

The nomenclature of the hepatic segments was that described by Healey and Schroy (1953).

Pathological appearances

Complete atrophy: The macroscopic appearances of complete atrophy of the left lobe of the liver are illustrated in *Figs*. 1 and 2. The affected lobe was shrunken, firm and pink and was well demarcated from the right lobe. It measured 5 × 3 × 2 cm and thus was approximately one-tenth-of the size of a normal left lobe. The gross appearances of right lobe or segmental atrophy were similar to these. The microscopic features are illustrated by an operative liver biopsy (*Fig*. 3) taken from the left lobe of the liver shown in *Figs*. 1 and 2. There is almost complete absence of hepatocytes, proliferation of small bile ducts, considerable fibrosis and a patchy inflammatory cell infiltrate. Similar features were seen in the other patients with different causes of complete atrophy.

Partial atrophy: The macroscopic appearances differed only in degree from those described for complete atrophy. Microscopically, the features were also similar, except that there was some preservation of hepatocytes surrounded by broad bands of fibrous tissue.

Patients

These patients have all been seen personally over the past 7 years. The diagnosis was made in all cases except one (*Case* 3, *see below*) at operation or at autopsy, or both. The final diagnoses in the 34 patients are shown in *Table I*; these diagnoses were established pathologically in all cases except *Case* 3. *Cases* 1, 14, 15, 23, 25, 26, 28, 30, 31 and 32 have been reported previously (Ham, 1974; Ham et al., 1978).

In the following sections the features in the various groups of patients are summarized, together with descriptions of illustrative cases.

Table I: FINAL DIAGNOSES IN THE 34 PATIENTS

Alcoholic liver disease	7
Chronic active hepatitis with cirrhosis	7
Hydatid disease	7
Cryptogenic cirrhosis	4
Carcinoma of right hepatic duct	2
Sclerosing cholangitis	2
Viral hepatitis with acute liver failure	2
Hepatocellular carcinoma	1
Secondary biliary cirrhosis	1
Congenital hepatic fibrosis	1
Total	34

Alcoholic liver disease

The features of the 7 patients with alcoholic liver disease are shown in *Table II*. Six of the 7 patients had alcoholic cirrhosis, 4 with portal hypertension and oesophageal varices; the remaining patient had alcoholic hepatitis without cirrhosis, and chronic pancreatitis. The right lobe was affected in 4 patients and the left lobe in 3. In *Case* 3 the diagnosis was made clinically; on abdominal examination the liver was markedly enlarged in the epigastrium but impalpable in the right hypochondrium. A liver scintiscan demonstrated that most of the liver tissue was in the epigastrium, and there was no evidence of a space-occupying lesion in this region. Coeliac and superior mesenteric angiography demonstrated a marked reduction in the number and size of the arterial branches supplying the right lobe of the liver. The venous phase films showed that the right branch of the portal vein was much smaller than the left. Hepatic venography did not demonstrate an outflow block in either lobe.

Chronic active hepatitis

These 7 patients (*Table III*) all had associated macronodular cirrhosis, and 4 had portal hypertension requiring a shunt procedure. The right lobe was affected in 4 patients and the left lobe in 3.

Case 12: The macroscopic and microscopic appearances of the liver in *Case* 12 are shown in *Figs*. 1–3. This patient had known chronic liver disease and presented with portal hypertension and bleeding oesophageal varices. A liver scintiscan demonstrated little remaining hepatic tissue in the epigastrium. A subtraction film from the arterial phase of a coeliac angiogram is shown in *Fig*. 4; there is a marked reduction in the size and

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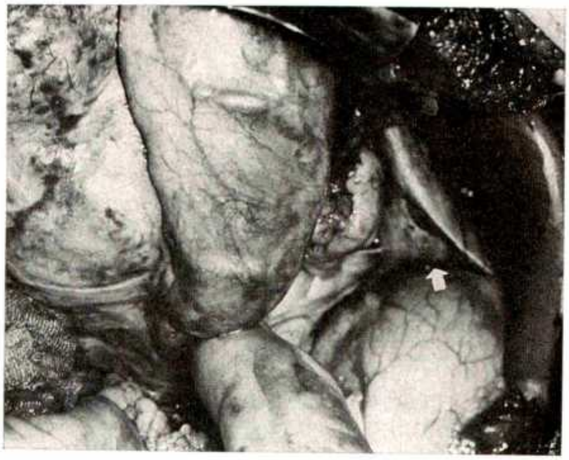

Fig. 1. Complete atrophy of the left lobe of the liver (arrow) in *Case* 12 demonstrated at operation. The gallbladder is in the centre of the picture.

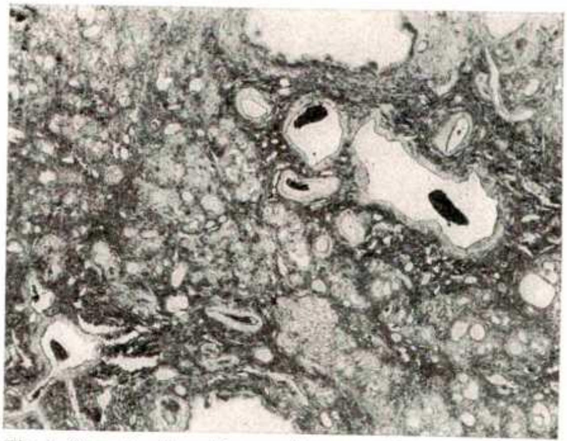

Fig. 3. Operative liver biopsy of the atrophic left lobe in *Case* 12. There is almost complete absence of hepatocytes (*see* text). (× 14.)

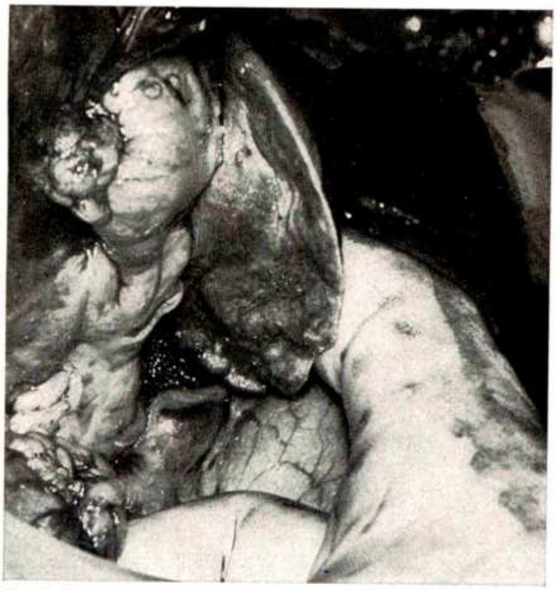

Fig. 2. Close-up view of the atrophic left lobe in *Case* 12.

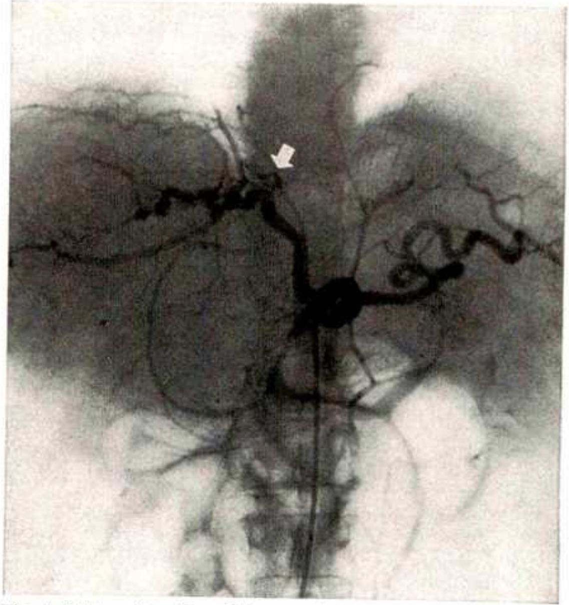

Fig. 4. Subtraction film of the arterial phase of a coeliac angiogram in *Case* 12. There is a marked reduction in the size and number of arteries supplying the region of the left lobe (arrow).

number of arteries supplying the region of the left lobe. In this patient, therefore, the diagnosis of complete left lobe atrophy was made preoperatively on the basis of these two investigations. The portacaval shunt procedure was technically difficult because of the gross distortion of the liver and displacement of the portal vein to the left away from the inferior vena cava.

Hydatid disease

These 7 patients had large single hydatid cysts in the right lobe (*Table IV*). Two patients had complete atrophy of all hepatic tissue in the right lobe and the remaining 5 had partial atrophy. In all 7 patients the left lobe was hypertrophied, this being most marked in the 2 with complete right lobe atrophy. In the latter patients, the left lobe was enlarged to the size of a normal liver.

Case 18: At operation *Case* 18 was found to have a large cyst (15 cm in diameter) in the upper part of the right lobe and what liver tissue remained in this lobe was shrunken. There was a sharp demarcation between the right and left lobes, partly because of the shrinkage of the right lobe and partly because of the enlargement of the left lobe. The liver scintiscan in this patient corresponded closely with these findings.

Cryptogenic cirrhosis (*Table V*)

Four patients had cryptogenic cirrhosis. *Case* 25 had complete atrophy of the medio-superior and medio-inferior segments of the left lobe, producing a deep cleft between the remaining left lobe segments and the right lobe. At autopsy this patient was found to have dilated bile ducts in these segments caused by a malignant hepatoma 5 cm in diameter arising in the quadrate lobe.

Carcinoma of right hepatic duct (*Table VI*)

Case 27, a woman of 22, presented with progressive obstructive jaundice. A percutaneous transhepatic cholangiogram demonstrated dilated ducts in the right lobe thought to be due to malignant obstruction of the right hepatic duct. The ducts were 'crowded' together, reduced in length and displaced to the right.

Table II: PATIENTS WITH ALCOHOLIC LIVER DISEASE

Case no.	Sex	Age (yr)	Affected part of liver	Partial or complete atrophy	Remainder of liver	Treatment
1	M	44	Left lobe	Complete	Enlarged, alcoholic hepatitis	Drainage of pancreatic abscess
2	F	63	Left lobe	Partial	Cirrhosis	Medical
3	M	57	Right lobe	Complete (?)	Cirrhosis	Medical
4	M	67	Right lobe	Partial	Cirrhosis	Portacaval shunt
5	M	54	Right lobe	Partial	Cirrhosis	Portacaval shunt
6	M	47	Right lobe	Partial	Cirrhosis	Portacaval shunt
7	M	46	Left lobe	Complete	Cirrhosis	Portacaval shunt

Table III: PATIENTS WITH CHRONIC ACTIVE HEPATITIS

Case no.	Sex	Age (yr)	Affected part of liver	Partial or complete atrophy	Remainder of liver	Treatment
8	M	72	Right lobe	Complete	Cirrhosis	Laparotomy only
9	M	51	Left lobe	Complete	Cirrhosis	Portacaval shunt
10	M	47	Right lobe	Partial	Cirrhosis	Medical
11	F	49	Right lobe	Partial	Cirrhosis	Exploration common bile duct
12	M	37	Left lobe	Complete	Cirrhosis	Portacaval shunt
13	F	58	Right lobe	Partial	Cirrhosis	Portacaval shunt
14	F	34	Left lobe	Complete	Cirrhosis	Portacaval shunt

Table IV: PATIENTS WITH HYDATID DISEASE

Case no.	Sex	Age (yr)	Affected part of liver	Partial or complete atrophy	Remainder of liver	Treatment
15	F	52	Right lobe	Complete	Hypertrophy	R hepatic lobectomy
16	F	21	Right lobe	Partial	Hypertrophy	Evacuation of cyst: omentopexy
17	F	19	Right lobe	Partial	Hypertrophy	Evacuation of cyst: omentopexy
18	F	47	Right lobe	Partial	Hypertrophy	Evacuation of cyst: omentopexy
19	F	34	Right lobe	Partial	Hypertrophy	Evacuation of cyst: omentopexy
20	M	59	Right lobe	Complete	Hypertrophy	Evacuation of cyst: partial liver excision
21	M	36	Right lobe	Partial	Hypertrophy	Evacuation of cyst: omentopexy

Table V: PATIENTS WITH CRYPTOGENIC CIRRHOSIS

Case no.	Sex	Age (yr)	Affected part of liver	Partial or complete atrophy	Remainder of liver	Treatment
22	F	55	Right lobe	Partial	Cirrhosis	Portacaval shunt
23	M	47	Left lobe	Complete	Cirrhosis	Portacaval shunt
24	F	59	Left lobe	Partial	Cirrhosis	Portacaval shunt
25	M	49	Medio-superior and medio-inferior segments left lobe	Complete	Cirrhosis, hepatoma in quadrate lobe	Cholecystectomy, exploration of common bile duct

Table VI: MISCELLANEOUS GROUP

Case no.	Sex	Age (yr)	Diagnosis	Affected part of liver	Partial or complete atrophy	Treatment
26	F	59	Carcinoma right hepatic duct	Right lobe	Complete	Laparotomy and biopsy
27	F	22	Carcinoma right hepatic duct	Right lobe	Partial	Right hepatic lobectomy
28	M	32	Sclerosing cholangitis	Latero-inferior segment left lobe	Complete	T tube drainage, steroids
29	M	62	Sclerosing cholangitis	Right lobe	Partial	T tube drainage, steroids
30	F	70	Viral hepatitis	Left lobe	Complete	Exchange blood transfusion
31	F	56	Viral hepatitis	Left lobe	Complete	Pig liver perfusion
32	F	30	Hepatocellular carcinoma	Right lobe	Partial	Right hepatic lobectomy
33	M	32	Secondary biliary cirrhosis (benign bile duct tumour)	Latero-inferior segment left lobe	Complete	Biliary bypass
34	M	16	Congenital hepatic fibrosis	Latero-inferior segment left lobe	Complete	Portacaval shunt

Subsequent films of the left lobe ducts demonstrated partial obstruction of the left hepatic duct at the junction of the right and left ducts. It was felt that resection of the tumour was possible, there being sufficient uninvolved left hepatic duct to carry out an anastomosis to a jejunal segment. At operation partial atrophy of the right lobe was found. A right hepatic lobectomy and resection of the tumour was performed.

Sclerosing cholangitis (*Table VI*)

One of these patients (*Case* 28) had atrophy of the latero-inferior segment of the left lobe and a T tube cholangiogram demonstrated obstruction of the bile duct draining that segment (Ham, 1974). The second patient (*Case* 29) presented with severe cholestasis. A percutaneous transhepatic cholangiogram demonstrated partial obstruction of the right hepatic duct and secondary obstructions of smaller ducts in the right lobe. The operative and pathological findings were compatible with the diagnosis of sclerosing cholangitis and there was partial atrophy of the right lobe of the liver.

Remaining patients

Case 32 had a large hepatocellular carcinoma in the upper part of the right lobe with partial atrophy of the remaining uninvolved liver tissue. The patient did not have cirrhosis, and there was evidence that the tumour may have been induced by oral contraceptives (Ham et al., 1978).

Case 33 presented with prolonged cholestasis. A percutaneous transhepatic cholangiogram was interpreted as demonstrating malignant obstruction at the ampulla. The operative findings included biliary cirrhosis, atrophy of the latero-inferior segment of the left lobe and a benign tumour at the lower end of the common bile duct. These findings were confirmed histologically.

The final patient (*Case* 34) presented with portal hypertension and bleeding oesophageal varices. The diagnosis of congenital hepatic fibrosis and segmental atrophy was confirmed by operative biopsy.

Summary of data

There were 17 patients with complete atrophy and 17 with partial atrophy. The lesion involved the right lobe in 20 patients, the left lobe in 10 and hepatic segments in 4. Segmental atrophy was only seen in the left lobe and was always complete.

There were 17 patients with cirrhosis due to primary hepatocellular disease (*Tables II, III* and *V*). The right lobe was atrophic in 9 of these patients and the left in 8. However, only 2 of the former group had complete atrophy, whereas complete atrophy was present in 6 of the 8 affected left lobes.

Hypertrophy of the unaffected hepatic segments or lobes was a striking feature in those patients with space-occupying lesions, i.e. hydatid cysts and hepatic tumours. It was much less common in those with cirrhosis or other diffuse hepatic disease.

Precise aetiological factors were difficult to determine in many patients. However, obstruction of the bile ducts draining the affected segment or lobe was demonstrated in the 2 patients with carcinomas of the right hepatic duct (*Cases* 26 and 27), the 2 patients with sclerosing cholangitis (*Cases* 28 and 29) and *Case* 25, who had cryptogenic cirrhosis and a hepatoma. There was no definite proof of vascular or biliary obstruction in any of the other patients.

Discussion

Benz et al. (1952) described liver atrophy as an incidental curiosity encountered at necropsy and Bockus (1965) suggested that it was of little clinical significance. By contrast, Braasch et al. (1972) have described 4 patients with strictures of bile ducts draining a liver segment or lobe and accompanying atrophy. Galloway et al. (1973) have demonstrated atrophy in unilobar venous outflow obstruction, and Hueston (1963) has reported atrophy in association with hydatid disease. There are also descriptions of liver atrophy in the various forms of cirrhosis (Baggenstoss and Stauffer, 1952; Benz et al., 1952). Thus, these reports and the experience with the present series of patients suggest that the condition is more common than is generally recognized.

It is also clear that the clinician treating patients with hepatobiliary disorders must have a knowledge of these abnormalities. The potential difficulties they may create in the interpretation of the findings on physical examination and the results of investigations are well illustrated by the patients presented here. It has been stressed by Soloway et al. (1971) and Scheuer (1973) that hepatic disease is frequently uneven in its distribution, which may result in significant sampling errors when hepatic disease is assessed by percutaneous needle biopsy. Atrophic lesions are clearly one cause of such sampling errors. The surgeon who observes these abnormalities during laparoscopy or laparotomy must be aware of their causes and significance in order to obtain the appropriate biopsies and plan the patient's management.

The findings in *Case* 3 illustrate that the diagnosis may be suspected on physical examination when hypertrophy of one lobe is associated with atrophy of the other. Most commonly, differential enlargement of the liver in the epigastrium or right hypochondrium will suggest an abnormality in that region of the liver, e.g. a Riedl's lobe, tumour or cyst. However, the enlargement may be caused by hypertrophy of the normal lobe while the abnormality is in the impalpable lobe. These were the physical findings in a number of patients in this series, notably those with hydatid disease and bile duct tumours.

With increasing experience, we have suspected the diagnosis more frequently on examining liver scintiscans, although only gross lesions are evident. There is usually little or no isotope uptake in an atrophic lobe and only patchy uptake in a partly atrophic region. However, in many of our patients the diagnosis could only be suspected, even when the scintiscans were reviewed with full knowledge of the diagnosis.

It was difficult to distinguish between the anatomical right and left lobe on the scintiscan of many of the cirrhotic patients because of liver distortion and the lack of an easily identifiable gallbladder impression. In the patients with hydatid disease the scintiscans were much easier to interpret, the findings being a large filling defect in the right lobe, little or no uptake in the remaining right lobe and the left lobe approximating the size of a normal liver. As might be expected, it was difficult to detect areas of segmental atrophy. However, atrophy of the medial segments of the left lobe was demonstrated in *Case* 25 (Ham, 1974). It is obviously important for those interpreting liver scintiscans to be aware that liver atrophy may produce an appearance compatible with that of a space-occupying lesion, and consequently a misdiagnosis of liver tumour may be made. This error occurred in 2 patients in this series.

Coeliac and superior mesenteric angiography with venous phase films provides much useful information and may be diagnostic in patients with complete lobar atrophy. Early in this series we failed to appreciate the changes demonstrated. In the more recent patients, however, we have recognized that lobar atrophy is associated with a reduction in the number of arteries supplying the affected lobe, and those arteries which are seen are 'crowded' and tortuous. Both arteries and veins are reduced in size, sometimes markedly (*see Fig.* 4). The affected region is relatively avascular. There may be displacement of the vessels in the unaffected lobe towards the affected side, and the unaffected lobe may be enlarged.

The bile ducts in an atrophic lobe may also be displaced to the affected side and 'crowded' together. Dilatation of the ducts is an important finding since the patient may have a surgically correctable lesion.

The causes of liver atrophy have been discussed in detail by Rous and Larimore (1920), Himsworth (1947) and by Schalm et al. (1956). These authors have stressed the great variety of possible causes, including vascular or bile duct obstruction and direct liver injury caused by viruses, toxins or nutritional factors. In some patients, more than one of these factors may be important.

The experimental studies of Schalm et al. (1956) on segmental and lobar biliary obstruction have demonstrated that such lesions are regularly accompanied by atrophy of the appropriate region of the liver and hypertrophy of the remainder. Thus, the pathological changes are similar to those in patients with obstruction of an intrahepatic bile duct. However, they are not identical, because the experimental models are usually created by acute ductal obstruction, whilst in man the clinical features are more often the result of progressive, slow biliary obstruction. Biliary obstruction was positively identified in 5 patients in this series (*Cases* 25, 26, 27, 28, 29). It was probably a factor in *Cases* 32 and 33 and in the 7 patients with hydatid disease. However, it is likely that the latter 9 patients had vascular obstruction as well.

The cause of the atrophy in the patients with primary hepatocellular disease is uncertain, but presumably it followed hepatic cell damage and necrosis. It is not clear, however, why the effect should be lobar or segmental. In addition, the left lobe seemed to be disadvantaged as compared to the right; segmental lesions were only observed in the left lobe and, although approximately equal numbers of patients had right and left lobe lesions, a greater proportion of the left-sided lesions was complete. This suggests that the left lobe may be more vulnerable to damage, or that its ability to recover following injury is impaired. The experiments of Starzl et al. (1973) have demonstrated the importance of the biochemical environment of different liver regions in maintaining hepatic homeostasis. Specifically, they demonstrated that the substances responsible for hepatic hypertrophy, hyperplasia, glycogenation and weight gain were derived from the pancreatic–gastroduodenal–splenic venous drainage. They concluded that these hepatotrophic substances were insulin and glucagon. An absolute or relative lack of these, or of other hepatotrophic factors, may have been important in the pathogenesis of the lesions seen in some of these patients.

Such a mechanism is not easy to understand in patients with diffuse hepatic disease, but it is possible that during the acute phase of liver injury the portal blood flow to certain regions of the liver may be compromised, perhaps due to acute liver enlargement. The combination of reduced portal blood flow and the factor causing the acute injury might result in liver cell necrosis and subsequent atrophy.

Whatever their cause, these lesions certainly indicate serious hepatic disease, either local or diffuse. Suggestions regarding treatment have been outlined previously (Ham, 1974) and it is stressed again that the only treatable causes of liver atrophy are those associated with bile duct obstruction or space-occupying lesions.

Acknowledgements

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References

BAGGENSTOSS A. H. and STAUFFER M. H. (1952) Posthepatic and alcoholic cirrhosis: clinicopathologic study of 43 cases of each. *Gastroenterology* 22, 157–180.

BENZ E. J., BAGGENSTOSS A. H. and WOLLAEGER E. E. (1952) Atrophy of the left lobe of the liver. *Arch. Pathol.* 53, 315–330.

BOCKUS H. L. (1965) *Gastroenterology*, 2nd ed. Philadelphia, Saunders.

BRAASCH J. W., WHITCOMB F. F., WATKINS E. et al. (1972) Segmental obstruction of the bile duct. *Surg. Gynecol. Obstet.* 134, 915–920.

GALLOWAY S., CASARELLA W. J. and PRICE J. B. (1973) Unilobar veno-occlusive disease of the liver. *Am. J. Roentgenol.* 119, 89–94.

HAM J. M. (1974) Segmental and lobar atrophy of the liver. *Surg. Gynecol. Obstet.* 139, 840–844.

HAM J. M., STEVENSON D. and LIDDELOW A. G. (1978) Hepatocellular carcinoma possibly induced by oral contraceptives. *Am. J. Dig. Dis.* 23, 38s–40s.

HEALEY J. E. and SCHROY P. (1953) The anatomy of the bile ducts within the human liver; an analysis of the prevailing patterns of branching and their major variants. *Arch. Surg.* 66, 599–616.

HIMSWORTH H. P. (1947) *Lectures on the Liver and its Diseases.* Cambridge, Mass., Harvard University Press.

HUESTON J. T. (1953) The production of liver lobe atrophy by hydatid cysts. *Br. J. Surg.* 41, 427–430.

ROUS P. and LARIMORE L. (1920) Biliary factor in liver lesions. *J. Exp. Med.* 32, 249–272.

SCHALM L., BAX L. R. and MANSENS B. J. (1956) Atrophy of liver after occlusion of bile ducts or portal vein and compensatory hypertrophy of unoccluded portion and its clinical importance. *Gastroenterology* 31, 131–155.

SCHEUER P. J. (1973) *Liver Biopsy Interpretation*, 2nd ed. London Baillière Tindall.

SOLOWAY R. D., BAGGENSTOSS A. H., SCHOENFIELD L. J. et al. (1971) Observor error and sampling variability tested in evaluation of hepatitis and cirrhosis by liver biopsy. *Am. J. Dig. Dis.* 12, 1082–1086.

STARZL T. E., FRANCAVILLA A., HALGRIMSON C. G. et al. (1973) The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. *Surg. Gynecol. Obstet.* 137, 179–199.

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Br. J. Surg. Vol. 66 (1979) 338–339

The treatment of major liver trauma by primary packing with transfer of the patient for definitive treatment

R. Y. CALNE, P. McMASTER AND B. D. PENTLOW*

SUMMARY

Four patients are reported in whom massive haemorrhage from severe hepatic trauma was managed initially by conservative surgery and packing. The patients were then transferred by ambulance to Addenbrooke's Hospital where further treatment involved elective surgery and removal of packs. All 4 patients were discharged from hospital and have made full recoveries. It is felt that the management of liver trauma should be to do the minimum that is necessary to staunch bleeding, by suture, arterial ligation, lobectomy, resectional débridement or simply by packing. This allows the patient's haemodynamic state to be restored to normal before further surgery is attempted.

THE incidence of major liver trauma is increasing (Aronsen et al., 1968; Walt, 1974). With an efficient ambulance service and improved methods of resuscitation, patients who would previously have died *en route* to hospital or in the accident service are surviving long enough for surgical treatment. In an excellent review on hepatic trauma, Walt (1978) refers to 5 patients who appeared to be exsanguinating before the insertion of packs, yet all recovered and were discharged from hospital. Even in large hospital centres with expert anaesthetists, continuous patient monitoring and unlimited supplies of banked blood, major hepatic trauma involving the hepatic veins and vena cava has an extremely high mortality (Wilson, 1963; Schrock et al., 1968). We report here a personal series of 4 consecutive cases referred to Addenbrooke's Hospital in whom massive exsanguinating haemorrhage could only be controlled by packing with gauze rolls. Undoubtedly, the patients owe their lives to this procedure, which enabled their safe transfer and subsequent management, so that all were able to leave hospital and return to normal health and full rehabilitation.

We endorse Walt's view that 'The judicious surgeon who choses this method should in no way fear the whispered loss of his surgical manhood' (Walt, 1978).

Case reports

Case 1: M. W., a male aged 16, was admitted on 3 June 1971. He had been sleeping in a field when his abdomen was crushed by the wheels of a Land Rover. Laparotomy revealed extensive lacerations to the right lobe of the liver. Attempts at haemostasis by suturing over Surgicel did not control the bleeding. The area around the liver was packed with gauze rolls and the patient was transferred to Addenbrooke's Hospital. On arrival 14 h after injury he had received 20 units of blood and was in a shocked state with a grossly distended abdomen. He was taken to theatre and the laparotomy incision was extended into the right chest, through the eighth intercostal space. A large amount of clotted and liquid blood was removed from the abdominal cavity. Most of the right lobe had been avulsed and was ischaemic. The hepatic artery and portal vein were cross-clamped and a right hepatic lobectomy was performed, the operation mainly consisting of removal of the necrotic liver and suturing of exposed blood vessels. Postoperative intensive care required bronchoscopy, mechanical ventilation for 48 h and repeated aspiration of pleural effusions. The patient was discharged from hospital 3 weeks after operation and has remained well.

When last seen on 4 October 1973 the liver scan showed regeneration over the liver to full size and the patient was leading a perfectly normal life as a member of the Royal Air Force.

Case 2: B. D., a female aged 36, was admitted on 16 December 1975 after having been knocked off her moped by a car. In addition to abdominal injuries, there were haematomas over the left orbit, chest, right arm and leg, the left little finger and wrist were fractured and there was a laceration of the right thigh. Laparotomy revealed 6 l of intraperitoneal blood and extensive lacerations into the right lobe of the liver.

Bleeding was controlled by packing the lacerations with Surgicel and gauze rolls and by hepatic arterial ligation beyond the gastroduodenal artery. By the time of admission to Addenbrooke's Hospital 24 h later she had received 28 units of blood. She was normotensive and passing urine, but had a pulse rate of 160 and CVP of -6 cmH$_2$O. Prothrombin time was 32 s (control 16 s), platelets 62×10^9/l, blood sugar 90 (5 mmol units).

After 18 h of intensive resuscitation with blood, platelets and fresh frozen plasma, laparotomy was performed extending the incision into the chest via the eighth intercostal space. A large quantity of old blood was removed, as were the packs There were deep lacerations in the right hepatic lobe, most of which was necrotic, as was the gallbladder. The left lobe was pale. Right partial hepatectomy was performed; removal of the ligature from the common hepatic artery did not produce pulsation. Arteriotomy revealed a fractured intima. This was repaired and the defect closed with a small patch taken from the right inferior epigastric artery. A good pulse was restored and the remaining liver took on a normal colour.

The patient required postoperative mechanical ventilation for 24 h. Liver function was temporarily deranged, the bilirubin rising to 162 μmol and the SGPT to 1152. The patient recovered from the other associated injuries.

When last seen on 1 March 1978, more than 2 years after the accident, the patient had normal liver function, no neurological defects and was in excellent health.

Case 3: T. v. N. a male aged 34, was admitted on 8 October 1974. He had developed signs of severe blood loss after suffering an upper abdominal stab wound. Laparotomy revealed a severe penetrating wound in the liver. Bleeding was temporarily controlled, but continued haemorrhage necessitated a further operation 24 h later. Bleeding was controlled by insertion of packs into a necrotic area in the right lobe of the liver. The patient was transferred to Addenbrooke's Hospital. The old wound was reopened and the incision was extended into the chest via the ninth intercostal space. The knife had penetrated the right lobe, within which was a large cavity containing blood clot. The liver superficial to this was of doubtful viability The haematoma was evacuated, some débridement performed and haemostasis secured. Large drains were inserted into the cavity.

Artificial ventilation was necessary for 24 h but events thereafter were relatively smooth. When the patient was last seen on 17 September 1975 there was no residual disability. One year after admission a liver scan showed a 5-cm 'scarred' area in the right lobe. The patient had returned to work.

Case 4: S. A., a male aged 22, was admitted on 15 September 1976 after being involved in a collison whilst riding a motor cycle. He had sustained abdominal injuries. Laparotomy revealed a massive haemoperitoneum with bleeding continuing from a tear in the gallbladder bed and porta hepatis. There was a hole in the portal vein. Bleeding was controlled by suture of the portal vein; the gallbladder was removed. Postoperative recovery was complicated by a pleural effusion thought to be secondary to a subphrenic abscess. Three weeks after injury the patient suddenly collapsed in a state of shock. At re-exploration blood welled up from the porta hepatis. Bleeding was controlled by packing and the patient was transferred, still under general anaesthesia, to Addenbrooke's Hospital where the wound was reopened. Two litres of blood clot were removed from around the liver. The principal site of bleeding was a 5-mm hole in the anterior wall of the portal vein, which was repaired with Prolene sutures. Bleeding from the tear into the liver stopped after evacuation of clot. An unidentified biliary radical was damaged during exploration, and because of this a T tube was inserted into the common bile duct. Drains were inserted into the hepatic laceration. After mechanical ventilation for 24 h the patient's course was uneventful. The T tube was left *in situ* for 9 weeks.

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When last seen on 21 June 1978 there was no residual disability and the patient had returned to work.

Discussion

These 4 patients all had potentially lethal hepatic injuries. Primary surgical treatment did not stop the haemorrhage and packing was resorted to as a life-saving procedure. The fact that the patients survived the packing and were transferred to Addenbrooke's Hospital implies selection, but they were all gravely ill and had suffered from severe blood loss. In this period from 1971 to 1978 there have been no other patients similarly treated by packing and then referred to the Department of Surgery in Cambridge who have failed to survive the journey. It has been our policy to attempt early definitive surgery on patients admitted primarily to our hospital with massive haemorrhage from the liver. An unsuccessful outcome has most often been due to hepatic venous bleeding. Death has rapidly followed laparotomy, presumably owing to release of the blood clot tamponade of the venous tear, following relaxation of the abdominal muscles and the abdominal incision.

From a consideration of the cases reported here, it would appear that there is a marked advantage to a patient who has sustained massive haemorrhage from liver trauma if a period for resuscitation can be achieved. During the course of a few hours, if rapid bleeding has been contained, blood loss can be replaced and the patient's haemodynamic equilibrium restored, before any further surgical intervention. Madding and Kennedy (1965) cautioned against packing liver injuries. Most of their cases were penetrating war wounds, often treated after considerable delay when sepsis was already established. We feel that with civilian casualties and rapid transfer to hospital the danger of sepsis in the presence of packs and devitalized liver tissue is less of a risk than continuing primary haemorrhage during emergency definitive surgery.

Conclusions

We believe that the management of liver trauma should be as conservative as possible. At laparotomy suture of lacerated liver and ligation of bleeding vessels is the first procedure. Bleeding from infrahepatic caval injuries can usually be controlled by direct suture. If arterial bleeding continues, selective hepatic artery ligation is undertaken distal to the gastroduodenal artery and cholecystectomy may be necessary. If, after suturing the lacerations, there is continuous venous bleeding from deep traumatic clefts which may involve the retroperitoneal vena cava, then large rolls of gauze are inserted into the depth of the wound without any further dissection of ligamentous attachments of the liver. The aim is to secure tamponade of venous lacerations. If this succeeds in stabilizing the patient's condition, the wound is closed and monitoring continued in the intensive care unit with a view to removing the packs and performing further laparotomy with removal of devitalized tissue, wound drainage and possible hepatic resection 2–3 days later. Broad spectrum antibiotics are administered systemically. If bleeding is not controlled by ligation and/or packing, the scale of the operation escalates, so that it becomes a major procedure. A definitive major lobar resection may succeed in saving a patient with trauma confined to one lobe. A tear of the hepatic veins or of the vena cava close to the hepatic veins can be extremely difficult to control because of bleeding preventing the lesion from being seen. To obtain a bloodless field the hepatic arterial and portal venous inflow must be clamped and the vena cava above and below the liver controlled (McMaster, 1977). Access to the cava above the liver can be obtained via the pericardium by splitting the sternum, and venous shunts may be required (Miller, 1972; Trunkey et al., 1974). This type of heroic surgery has an extremely high mortality even in skilled hands, but a successful outcome is possible (Waltuck et al., 1970).

On the basis of this limited experience from the cases reported here, we consider that the most important objective is to secure primary control of haemorrhage, whether by suture, hepatic arterial ligation, lobectomy, resection débridement or temporary packing. This permits a period of resuscitation which may be all important to the patient's life.

Acknowledgements

We thank the surgeons who referred these cases and all our medical, nursing and technician colleagues who assisted in their care.

References

ARONSEN K. F., BENGMARK S., DAHLGREN S. et al. (1968) Liver resection in treatment of blunt injuries to the liver. *Surgery* **63**, 236–264.

MCMASTER P. and TOLLEY M. (1977) Management of inferior vena cava injury in liver trauma. *Ann. R. Coll. Surg.* **59**, 502–506.

MADDING G. F. and KENNEDY P. A. (1965) *Trauma to the Liver*. Philadelphia, Saunders. (*Major Problems in Clinical Surgery*, III.)

MILLER D. R. (1972) Median sternotomy extension of abdominal incision for hepatic lobectomy. *Ann. Surg.* **175**, 193–196.

SCHROCK T., BLAISDELL F. W. and MATHEWSON C. (1968) Management of blunt trauma to the liver and hepatic veins. *Arch. Surg.* **96**, 698–704.

TRUNKEY D. D., SHIRES G. T. and MCCLELLAN R. (1974) Management of liver trauma in 81 consecutive patients. *Ann. Surg.* **179**, 722–728.

WALT A. J. (1974) Hepatic trauma. In: R. SMITH (ed.) *Surgical Forum—The Liver*. London, Butterworths, pp. 83–112.

WALT A. J. (1978) The mythology of hepatic trauma—or Babel revisited. *Am. J. Surg.* **135**, 12–18.

WALTUCK T. L., CROW R. W., HUMPHREY L. T. et al. (1970) Avulsion injuries of the vena cava following blunt abdominal trauma *Ann. Surg.* **171**, 67–72.

WILSON D. H. (1963) Incidence, aetiology, diagnosis and prognosis of closed abdominal injuries: a study of 265 consecutive cases. *Br. J. Surg.* **50**, 381–388.

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Postoperative hypophosphataemia

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SUMMARY

The possible mechanisms of postoperative hypophosphataemia were studied in women undergoing uncomplicated cholecystectomy. Six patients were allocated to each of three groups. Group I received no intravenous fluids, group II received dextrose/saline solution alone and group III received dextrose/saline solution with phosphorus supplementation. The serum concentration of inorganic phosphorus fell in all three groups, the greatest fall being in the group receiving dextrose/saline solution. However, the lowest level reached (0·82 mmol/l) was within the normal range for our laboratory. Concentrations of red blood cell adenosine triphosphate and 2,3-diphosphoglycerate showed similar changes. The operations were not associated with a large catabolic response nor with an increase in urinary phosphorus excretion. The postoperative reduction in serum concentration of inorganic phosphorus appeared to be due mainly to haemodilution. There is no indication for routine phosphorus supplementation following uncomplicated elective surgery.

HYPOPHOSPHATAEMIA reduces the content of 2,3-diphosphoglycerate and adenosine triphosphate in red blood cells (Travis et al., 1971). As a consequence, haemoglobin has an increased affinity for oxygen and this hinders the release of oxygen in the tissues. Hypophosphataemia may also produce a severe haemolytic anaemia (Jacob and Amsden, 1971; Klock et al., 1974). Both these mechanisms contribute to dangerous tissue hypoxia. Hypophosphataemia is a well-recognized complication of intravenous feeding regimens containing high concentrations of dextrose (Groen et al., 1952; Travis et al., 1971), chronic alcoholism (Territo and Tanaka, 1974), septicaemia (Riedler and Schietlin, 1969), and in patients undergoing renal dialysis (Mahony et al., 1976). Hypophosphataemia has been reported recently following the routine postoperative infusion of dextrose/saline solution (Guillou et al., 1976). However, the plasma inorganic phosphorus concentration fell not only in patients who received dextrose/saline but also in those who received saline alone, and rose again to preoperative concentrations despite the continuation of the infusion. These observations suggested that some factor other than the dextrose infusion was contributing to the hypophosphataemia. Furthermore, the clinical significance of these findings is uncertain as the concentration of plasma inorganic phosphorus did not fall to levels associated with clinical signs or symptoms, and red blood cell concentrations of 2,3-diphosphoglycerate and adenosine triphosphate were not measured. It is these organic, intracellular compounds that are of importance in inducing changes in the oxygen dissociation curve (Travis et al., 1971).

This study was undertaken to examine the possible mechanisms of hypophosphataemia in women following elective cholecystectomy and to ascertain whether this has any clinical significance.

Patients and methods

Eighteen female patients undergoing elective cholecystectomy without exploration of the common bile duct were admitted 48 h before surgery and their informed consent to the study was obtained. None of the patients studied was taking the contraceptive pill or other hormonal preparation. Six patients were allocated to each of three groups. Group I patients received no intravenous infusion; group II patients received 2·5 l of 4 per cent dextrose and 0·18 isotonic saline and 40 mmol of potassium chloride; and group III patients received 2·5 l of 4 per cent dextrose and 0·18 per cent isotonic saline, 10 mmol of potassium chloride and 30 mmol of potassium dihydrogen phosphate. Samples of venous blood were taken preoperatively and postoperatively at the end of each 24-h period of study. Similarly, 24-h collections of urine were obtained. The samples were analysed on Technicon SMA 12/60 and SMA 6/60 analysers for serum inorganic phosphorus and calcium, serum and urinary urea and creatinine, serum albumin and packed cell volume. Urinary calcium and phosphorus assays were performed manually. Phosphorus

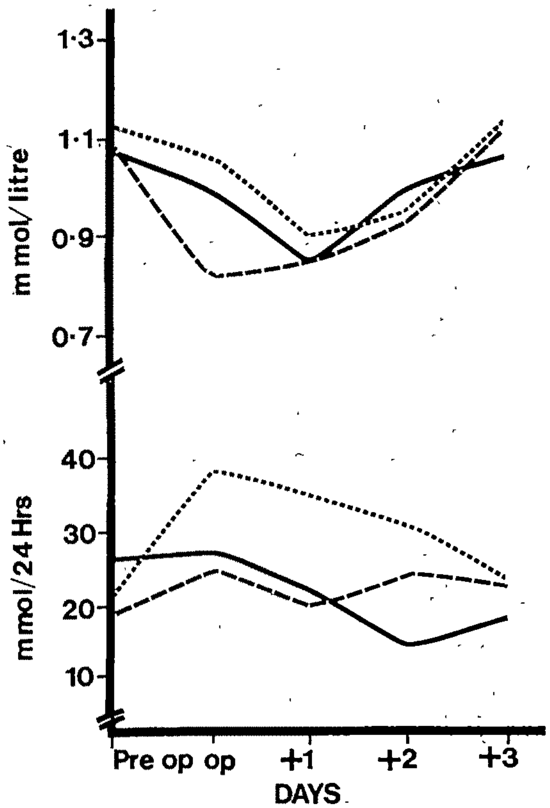

Fig. 1. The serum (top) and urinary (bottom) concentrations of inorganic phosphorus following surgery in the three groups studied.

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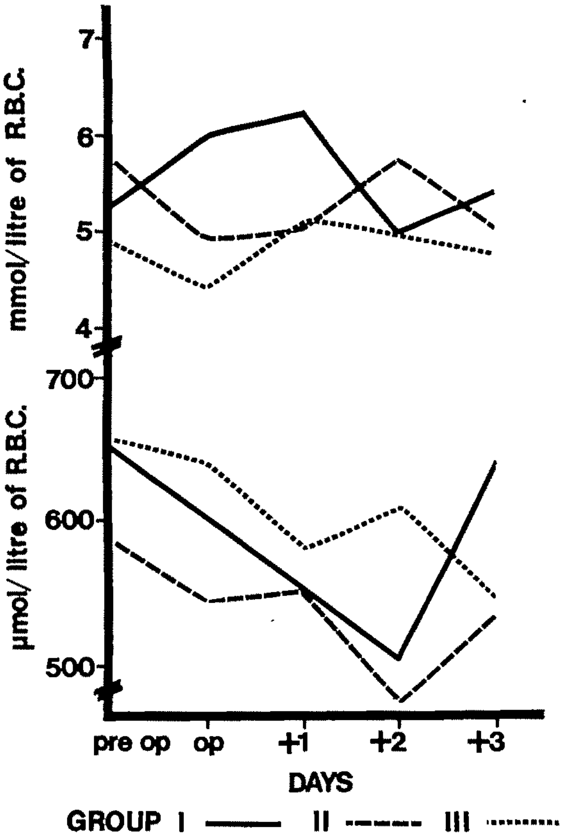

Fig. 2. The red blood cell concentrations of 2,3-diphosphoglycerate (top) and adenosine triphosphate (bottom) following surgery in the three groups studied.

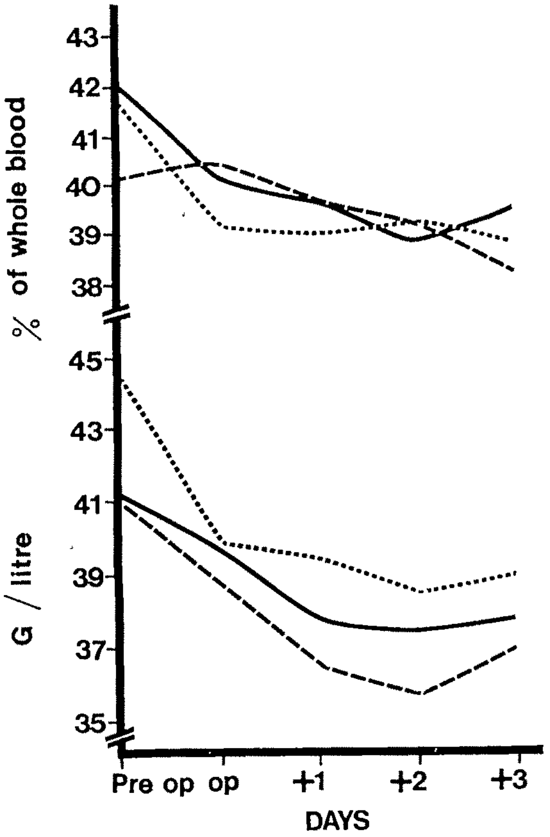

Fig. 3. The packed cell volumes (top) and serum concentrations of albumin (bottom) following surgery in the three groups studied.

determination was by the molybdovanadate method. Red blood cell content of 2,3-diphosphoglycerate and adenosine triphosphate was estimated using commercial kits (Boehringer Mannheim GmbH).

The 24-h periods of study have been designated preop. (preoperative), op. (day of operation) and day+1 to day+3 (postoperative). The results were analysed using Student's *t* test for paired data within the groups and Student's *t* test for unpaired data between the groups.

Results

The three groups studied were comparable in age and weight distribution. The mean (and standard deviation) ages and weights of the patients were: in group I, 45·7±15·6 years and 57·5±6·8 kg; for group II, 46·5±21 years and 67·2±10 kg; and for group III, 55·2±6·7 years and 63·2±14 kg.

Serum concentrations of inorganic phosphorus fell in all three groups, reaching the lowest value of 0·82 mmol/l on the day of operation in group II and on day+1 in groups I and III (*Fig.* 1). These falls were statistically significant in all groups when compared with the respective preoperative concentrations ($P<0{\cdot}05$). Following these falls, the concentrations of inorganic phosphorus rose, regaining preoperative concentrations by day+3. The only significant difference between the groups was on the day of operation, when the concentration in group II was significantly lower than that in the other two groups ($P<0{\cdot}05$). There were small and divergent fluctuations in the red blood cell concentration of 2,3-diphosphoglycerate in all groups. In group II there were significant falls in the concentration on the day of operation, on day+1 and day+3 when compared with the preoperative concentration ($P<0{\cdot}01$). There were no intergroup differences. The red blood cell concentration of adenosine triphosphate fell in all groups (*Fig.* 2) and reached statistical significance in groups I and II ($P<0{\cdot}05$). On day+2 the fall in concentration of adenosine triphosphate in group II was significantly greater than that in group III ($P<0{\cdot}01$). The concentration of serum albumin fell in the three groups, reaching significance on day +1 to day+3 ($P<0{\cdot}01$). There were no significant differences between the groups. The packed cell volume also fell in the three groups studied (*Fig.* 3) but, owing to the wide range of results, this reached significance only in group I on day+1 and day+2 ($P<0{\cdot}05$). The concentration of serum urea rose in patients in group I who did not receive intravenous fluids but fell in the two groups that did, reaching significance in group III on day+1 to day+3 ($P<0{\cdot}01$). Serum concentrations of creatinine followed a similar trend. There were no significant changes in the concentration of serum calcium in any of the groups studied. There was no increase in the urinary excretion of inorganic phosphorus in groups I and II but in group III, who received phosphorus supplementation, there was a marked increase (*Fig.* 1), reaching

Table I: THE PREOPERATIVE, OPERATIVE AND POSTOPERATIVE CONCENTRATIONS OF SERUM AND URINARY INORGANIC PHOSPHORUS AND RED BLOOD CELL CONCENTRATIONS OF 2,3-DPG AND ATP IN THE THREE GROUPS STUDIED

	Group	Preop.	Op. day	Day+1	Day+2	Day+3
Serum phosphorus (mmol/l, mean±s.d.)	I	1·07±0·14	1·00±0·13	0·85±0·13*	1·00±0·2	1·07±0·11
	II	1·08±0·11	0·82±0·11*	0·85±0·11**	0·93±0·16	1·12±0·19
	III	1·13±0·075	1·07±0·16	0·90±0·13**	0·95±0·17	1·13±0·14
2,3-DPG (mmol/l RBC, mean±s.d.)	I	5·25±0·99	5·97±2·14	6·23±2·2	4·98±0·79	5·40±1·01
	II	5·78±0·38	4·9±0·48**	5·04±0·58**	5·76±0·26	5·09±0·45*
	III	4 9±0·43	4·43±0·7	5·11±0·34	4·97±1·02	4·76±1·09
ATP (μmol/l RBC, mean±s.d.)	I	652±60	598±249	559±180	505±124*	636±180
	II	582±49	542±78	554±37	475±37*	532±63
	III	656±88	640±129	578±86	609±94	547±111
Urinary inorganic phosphorus (mmol/24 h, mean±s.d.)	I	25·8±6·7	27·0±6·3	22·5±9·05	14·3±4·96*	18·3±16·3
	II	18·5±7·3	24·5±5·74	19·3±11·6	24·3±13·9	22·0±13·5
	III	21·8±4·9	38·4±14·4*	35·1±11·3*	31·03±13·3	23·9±9·3

2,3-DPG, 2,3 diphosphoglycerate; ATP, adenosine triphosphate.
* $P<0·05$; ** $P<0·01$.

Table II: THE PREOPERATIVE, OPERATIVE AND POSTOPERATIVE CONCENTRATIONS OF SERUM ALBUMIN AND THE PACKED CELL VOLUMES IN THE THREE GROUPS STUDIED

	Group	Preop.	Op. day	Day+1	Day+2	Day+3
Serum albumin (g/l, mean±s.d.)	I	41·3±4·1	39·7±3 6	37·7±3·25**	37·1±3·1**	37·8±3·7**
	II	41·0±2·8	38·8±3·5	36·7±1·6*	35·8±2·5*	37·0±3·8
	III	44·5±2·9	39·8±4·1**	39·5±3·3**	38·5±3·3**	39·0±2·4**
Packed cell volume (% whole blood, mean±s.d.)	I	42·0±3·0	40·2±3·2	39·7±1·9*	38·8±1·34*	39·5±1·7
	II	40·2±1·9	40·5±1·7	39·7±2·1	39·3±2·1	38·2±1·6
	III	41·7±3·3	39·2±3·8	39·0±3·2	39·3±2 4	38·8±2·6

* $P<0·05$; ** $P<0·01$.

significance on the day of operation and day+1 ($P<0·05$). There were no significant changes in the urinary excretion of urea, creatinine or calcium in any of the groups studied.

Discussion

The concentration of serum inorganic phosphorus fell significantly after surgery in all groups, indicating that some mechanism other than the simple postoperative infusion of dextrose fluids was responsible. The greatest fall, however, did occur in the group receiving dextrose/saline solution alone, but the concentrations were still well within the normal range for this laboratory and not as low as those reported by others (Guillou et al., 1976). In keeping with other reports (Guillou et al., 1976; Rowlands and Giddings, 1976), the concentration of serum inorganic phosphorus had reached preoperative values within 3–4 days of operation. Postoperative hypophosphataemia in well-nourished patients would appear to be a transient and self-limiting phenomenon and probably of little clinical significance. Further, the small falls in the red blood cell concentration of 2,3 diphosphoglycerate and adenosine triphosphate found in this study were within the normal range and unlikely to cause any significant shift to the left of the oxygen dissociation curve. There was no increase in the urinary excretion of inorganic phosphorus in the two groups that did not receive phosphorus supplementation.

Similarly, there was no increase in the urea excretion, indicating little protein catabolism following these elective operations. The group that received phosphorus supplementation had a large increase in urinary excretion of phosphorus. Although the overall phosphorus balance was improved when compared with the other two groups, it was still negative. Serum albumin and packed cell volume estimations are indicators of haemoconcentration and, in view of the insignificant operative and postoperative loss, the results suggest that a moderate degree of haemodilution occurred in all three groups.

The postoperative falls in the group that received no intravenous fluid were surprising. It has been reported that postoperative haemodilution is a consequence of water retention (Le Quesne, 1954). However, this group had an oral intake of approximately 300 ml and 600 ml of water and a mean urinary output of 575±217 and 732±439 ml respectively in the first two 24-h periods of study. In these starving patients the amount of water released by catabolism of body tissue (probably about 500 ml per day) would be exceeded by insensible water loss (probably about 1000 ml per day) so that there would be a negative water balance of 500–1000 ml per day. Thus, the haemodilution would appear to indicate a fluid shift from the intracellular space to the extracellular space.

The movement of water into and out of cells is determined by osmosis and governed by the relative concentrations of osmotically active particles on either side of the membrane. Any major shift of water out of the cell would be as a consequence of a loss of osmotically active particles, of which potassium is the major constituent.

An increased concentration of potassium in the serum and excretion of potassium in the urine are well-recognized events after surgery and this was observed in these patients. It has been suggested that an

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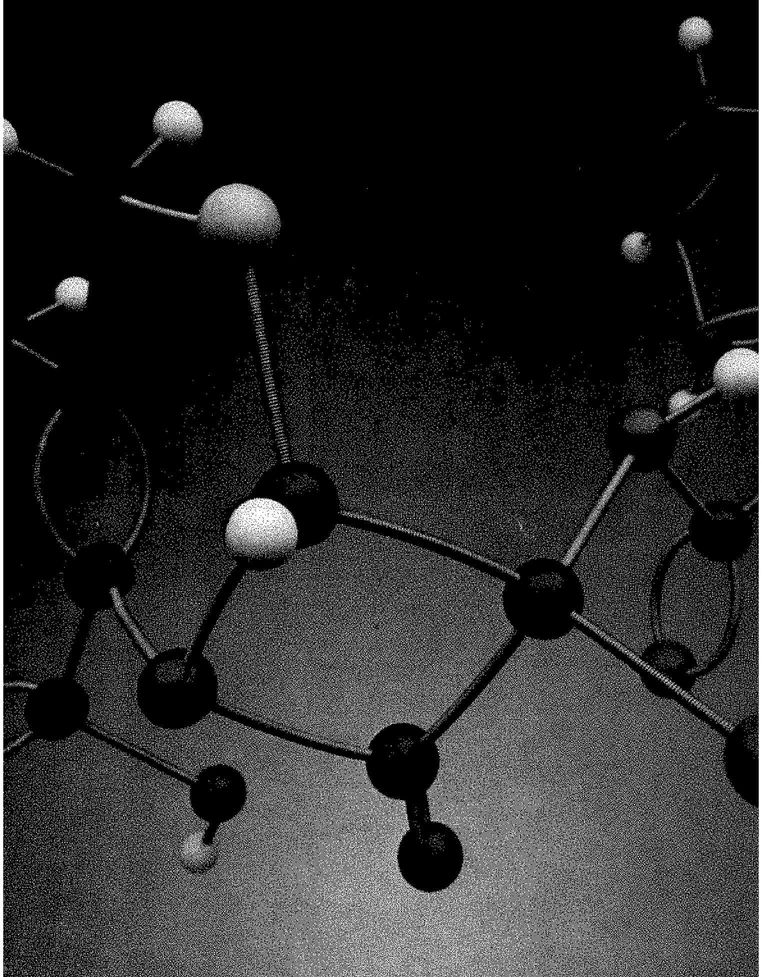
First of the cephamycins

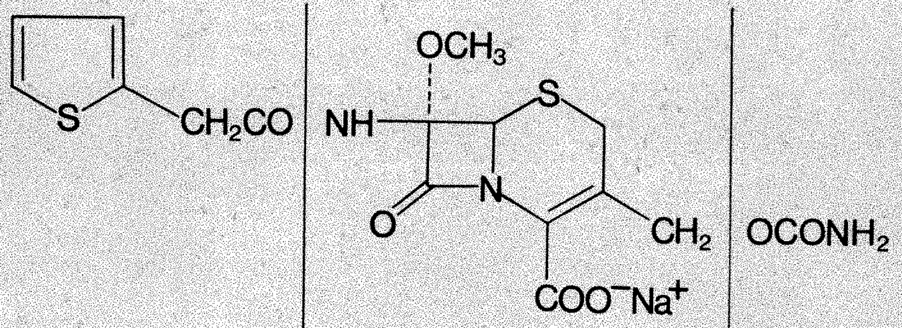


A new class of antibiotics

'Mefoxin' is derived from cephamycin C, a naturally antibiotic substance produced by *Streptomyces* *durans*. This naturally occurring antibiotic has been modified MSD Research Laboratories to enhance its therapeutic usefulnes

Prescribing information overleaf

'Mefoxin' has a unique molecular structure offering outstanding clinical benefits and a specific clinical profile.



Thienylacetyl side-chain:

enhances activity against Gram-positive pathogens

Cephamycin nucleus:

provides bactericidal activity against a wide range of pathogens, Gram-negative in particular. 7α-methoxy group protects against β-lactamase degradation

Carbamoyloxy side-chain:

protects antibiotic from being metabolised

▼Prescribing information

Indications

'Mefoxin' is a broad-spectrum bactericidal antibiotic indicated for the treatment of infections caused by susceptible strains of Gram-positive and Gram-negative pathogens both aerobic and anaerobic.

'Mefoxin' has been clinically effective not only in infections due to antibiotic-sensitive organisms, but also in infections due to organisms resistant to one or more of the following antibacterial agents: penicillin, ampicillin, carbenicillin, tetracyclines, erythromycin, chloramphenicol, cephalosporins, kanamycin, gentamicin, tobramycin, and sulphamethoxazole-trimethoprim.

Many Gram-negative pathogens are resistant to penicillins and cephalosporins through the action of the β-lactamases which are produced by these pathogens. 'Mefoxin' is remarkably stable in the presence of these bacterial β-lactamases, both penicillinases and cephalosporinases. Hence, the clinical efficacy of 'Mefoxin' extends to many infections caused by such pathogens.

'Mefoxin' is indicated for the treatment of the following infections caused by sensitive bacteria:
Peritonitis and other intra-abdominal and intrapelvic infections; female genital tract infections; septicaemia; urinary tract infections; respiratory tract infections; bone and joint infections; and skin and soft-tissue infections.

'Mefoxin' is indicated for adjunctive therapy in the surgical treatment of infections, including abscesses, infection complicating hollow visceral perforations, cutaneous infections, and infections of serous surfaces, whether caused by aerobes, mixed aerobes and anaerobes, or anaerobes.

Microbiology

'Mefoxin' is active *in vitro* against:

Aerobic bacteria

Gram-positive cocci including: Staphylococci: (including coagulase-positive, coagulase-negative, and penicillinase-producing strains); Group A beta-haemolytic streptococci *(Streptococcus pyogenes);* Group B beta-haemolytic streptococci *(Streptococcus agalactiae); Streptococcus pneumoniae (Diplococcus pneumoniae);* other streptococci (except group D streptococci including enterococci, most strains of which are resistant, e.g. *Streptococcus faecalis*). *Gram-negative cocci* including: *Neisseria gonorrhoeae* (including penicillinase-producing strains); *Neisseria meningitidis. Gram-negative rods (facultative anaerobes)* including: *Escherichia coli, Klebsiella pneumoniae;* Klebsiella spp.; *Proteus mirabilis. Proteus* (indole-positive): *Proteus vulgaris; Proteus rettgeri; Proteus morganii; Haemophilus influenzae; Serratia marcescens;* Providencia spp.; Salmonella and Shigella spp.

Anaerobic bacteria

Gram-positive cocci including: Peptococcus spp.; Peptostreptococcus spp.; Micro-aerophilic streptococcus. *Gram-positive rods including: Clostridium perfringens;* Clostridium spp.; Eubacterium spp.; *Propionibacterium acnes. Gram-negative cocci including:* Veillonella spp. *Gram-negative rods including: Bacteroides fragilis; Bacteroides melaninogenicus;* Bacteroides spp. (including both penicillin-susceptible and penicillin-resistant strains); Fusobacterium spp.

'Mefoxin' is active against some strains of the following bacteria: *Acinetobacter calcoaceticus var. anitratum (Herellea vaginicola); Acinetobacter calcoaceticus* var. *lwoffi (Mima polymorpha); Alcaligenes faecalis;* Citrobacter spp. and Flavo-bacterium spp.; Enterobacter spp.

'Mefoxin' is not active against Pseudomonas, most strains of enterococci and many strains of *Enterobacter cloacae.*

Dosage and administration

'Mefoxin' may be administered intravenously or intramuscularly. (See reconstitution directions for each route below.) Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organisms, and condition of the patient.

Therapy may be started while awaiting the results of susceptibility testing.

Dosage: The usual adult dosage is 1 g or 2 g of 'Mefoxin' every eight hours. (See chart.)

In adults with renal insufficiency, an initial loading dose of 1 g or 2 g may be given. After a loading dose, the following recommendations for *maintenance dosage* may be used as a guide.

Usual adult dosage

Type of infection	Dose	Frequency	Total daily dosage
Uncomplicated	1 g	Every 8 hours (occasionally every 6 hours)	3 g (4 g)
Moderately severe or severe	2 g	Every 8 hours (occasionally every 6 hours)	6 g (8 g)
Infections generally needing antibiotics in higher dosage	3 g (2 g)	Every 6 hours (Every 4 hours)	12 g

Maintenance dosage of 'Mefoxin' in adults with reduced renal function

Renal function	Creatinine clearance (ml/min)	Dose	Frequency
Mild impairment	50-30	1-2 g	Every 8-12 hours
Moderate impairment	29-10	1-2 g	Every 12-24 hours
Severe impairment	9-5	0·5-1 g	Every 12-24 hours
Essentially no function	<5	0·5-1 g	Every 24-48 hours

In the patients undergoing haemodialysis, the loading dose of 1 to 2 g should be given after each haemodialysis, and the maintenance dose should be given as indicated in the table above.

Intravenous administration: reconstitute 'Mefoxin' with Water for Injection BP: 1 g is soluble in 2 ml. Although 'Mefoxin' is very soluble, for intravenous use it is preferable to add 10 ml of Water for Injection BP to the 1 g vial or the 2 g vial. Shake to dissolve and then withdraw entire contents of vial into syringe.

For direct intravenous injection, 'Mefoxin' may be slowly injected into

Outstanding clinical benefits

Wide-ranging activity against Gram-negative and Gram-positive pathogens, anaerobes as well as aerobes.

Unusually high resistance to β-lactamase degradation.

Highly active against *Bacteroides fragilis* and strains of *E. coli*, Serratia, Klebsiella spp. and Proteus spp. (including indole positive strains) resistant to other antibacterial agents.

Offers high levels of active antibiotic in the body.

A record of relative safety comparable to the penicillins.

Prime indications include:

- Peritonitis, and other intra-abdominal and intrapelvic infections.
- Female genital tract infections
- Septicaemia
- Skin and soft tissue infections
- Bone and joint infections
- Urinary tract infections
- Respiratory tract infections (e.g. inhalation pneumonia)

Specific clinical profile

'Mefoxin' is exceptionally valuable wherever Gram-negative pathogens and anaerobes are involved in mixed infections. When mixed infections are suspected, therapy may be started while awaiting the results of susceptibility testing.

Mefoxin®

Cefoxitin sodium, MSD

INJECTION

First of the cephamycins

the vein over a period of 3 to 5 minutes or may be given through the tubing when the patient is receiving parenteral solutions.

An intermittent intravenous infusion of 'Mefoxin' may be employed when large amounts of fluid are to be given. However, during infusion of the solution containing 'Mefoxin', it may be advisable temporarily to discontinue administration of any other infusion solution at the same site (by using an appropriate IV infusion set).

A solution of 'Mefoxin' may also be given by continuous intravenous infusion (see below for compatibility and stability).

Intramuscular administration ONLY

Reconstitute 'Mefoxin' 1 g with 2 ml of Water for Injection BP, or 0.5% or 1% lignocaine hydrochloride (without adrenaline) solution. 'Mefoxin' is given by deep injection into a large muscle mass. Avoid injection into a blood vessel.

Compatibility and stability

A solution of 'Mefoxin' in Water for Injection BP may be added to the following solutions: 0.9% Sodium Chloride Injection BP, 5% or 10% Dextrose Injection BP, Dextrose and Sodium Chloride Injection (5%/0.9%, 5%/0.45%, or 4.3%/0.18%), Lactated Ringer's Injection USP, 5% Dextrose in Lactated Ringer's Injection, 5% or 10% invert sugar in water, 10% invert sugar in saline solution, 4.2% Sodium Bicarbonate Injection BP, M/6 Sodium Lactate Injection BP.

'Mefoxin', as constituted to 1 g/10 ml with Water for Injection BP, Water for Injection BP preserved with parabens or benzyl alcohol, 0.9% Sodium Chloride Injection BP or 5% Dextrose Injection BP, maintains satisfactory potency for 24 hours at room temperature, for 96 hours under refrigeration, and for 13 weeks in the frozen state.

'Mefoxin' can be administered concomitantly with such antibiotics as gentamicin, tobramycin, carbenicillin or amikacin. When 'Mefoxin' is administered with another antibiotic, they should not be mixed in the same syringe.

Contra-indications

'Mefoxin' is contra-indicated in persons who have shown hypersensitivity to cefoxitin. In the absence of clinical experience, 'Mefoxin' should not be administered to patients who have shown hypersensitivity to cephalosporins.

Precautions

There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and other β-lactam antibiotics, penicillins, and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most β-lactam antibiotics.

Before therapy with 'Mefoxin', careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibiotics. 'Mefoxin' should be given cautiously to penicillin-allergic patients.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. If an allergic reaction to 'Mefoxin' occurs, the drug should be discontinued.

The total daily dosage should be reduced when 'Mefoxin' is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see 'Dosage and administration') because high and prolonged serum antibiotic concentrations can occur from usual doses.

Interference with laboratory tests

A false-positive reaction to glucose in the urine may occur with reducing substances but not with the use of specific glucose oxidase methods.

Use in pregnancy

Use of the drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the foetus due to 'Mefoxin'. There are no controlled studies with 'Mefoxin' in pregnant women.

Nursing mothers

'Mefoxin' is excreted in human milk.

Infants and children

Pending the outcome of clinical trials in progress, the conditions for use of 'Mefoxin' in infants and children remain to be defined.

Side effects

'Mefoxin' is generally well tolerated. Side effects rarely require stopping treatment and usually have been mild and transient.

Local reactions

Thrombophlebitis has occurred with intravenous administration. Pain induration and tenderness after intramuscular injections have been reported.

Allergic

Maculopapular rash, urticaria, pruritus, eosinophilia, fever and other allergic reactions have been noted rarely.

Gastro-intestinal

Diarrhoea has been reported rarely.

Blood

Transient leucopenia and neutropenia have been reported. Some individuals, particularly those with azotaemia, may develop positive direct Coombs tests during therapy with 'Mefoxin'.

Liver function

Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase have been reported rarely.

Kidney

Elevations in serum creatinine and/or blood urea levels have been observed. The role of 'Mefoxin' in changes in renal function tests is difficult to assess, since factors predisposing to pre-renal azotaemia or to impaired renal function usually have been present.

Presentation

In vials containing 1 g or 2 g of cefoxitin as the sodium salt. Each gram of cefoxitin contains approximately [illegible] mg ([illegible]) of sodium.

Product licence numbers: 1 g 0025/0130, 2 g [illegible]

Product authorisation numbers: 1 g PA 35/42/1, 2 g PA 35/42/2

Issued October 1978

Additional information is available to the medical profession on request.

Basic NHS cost is £[illegible] for the 1 g vial, and £[illegible] for the 2 g vial.

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Magnapen

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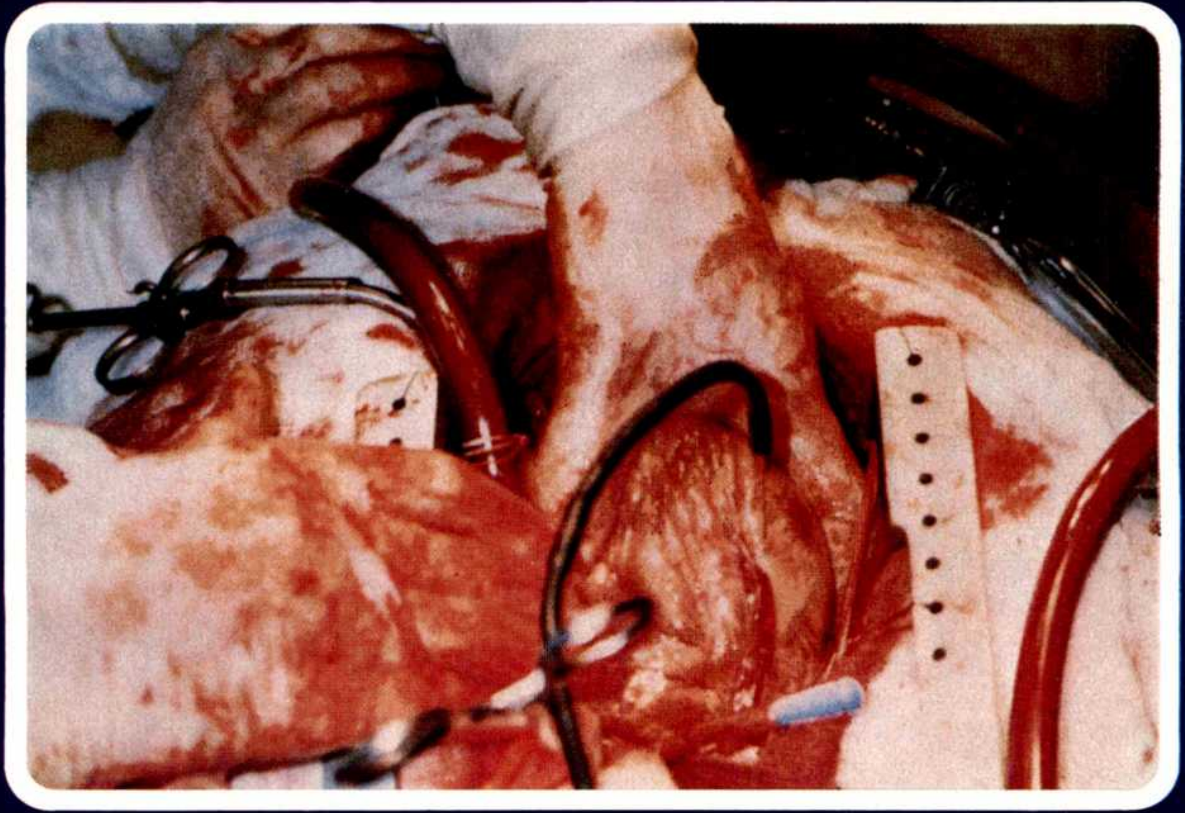

Reliable antibiotic cover for the at-risk patient.

In cardiothoracic surgery, infection poses a special threat. It is essential to reduce the risk to an absolute minimum with prophylactic antibiotic cover[1].

Magnapen is of proven value in prophylaxis. In a recent study of 221 patients undergoing thoracotomy for lung resection[2] of whom 181 received Magnapen cover, the author concluded that "There was a significantly reduced incidence of pneumonectomy space infection, post-operative pneumonia and wound infection after pneumonectomy and lobectomy in those patients receiving prophylactic antibiotics compared with those not receiving prophylactic antibiotics."

Magnapen combines the broad spectrum of ampicillin with the anti-staphylococcal activity of flucloxacillin. It can thus be relied on to eliminate virtually all strains of staphylococci[3,4], Strep. viridans[5] and other likely wound pathogens.

1. Brit. med. J. (1978), **1**, 1603
2. Thorax (1978), 33. **1**, 130
3. Brit. med. J. (1978), **2**, 536
4. Brit. med. J. (1970), **4**, 455
5. Zbl. Bakt. Hyg., I. Abt. Orig. A (1976), **236**, 235

Prescribing Information

Magnapen Capsules: Black and turquoise capsules overprinted "Magnapen" containing 250mg ampicillin as Ampicillin Trihydrate B.P. with 250mg flucloxacillin as flucloxacillin sodium.
Magnapen Syrup: Bottles containing powder for the preparation of 100ml suspension. When reconstituted each 5ml contains 125mg ampicillin as Ampicillin Trihydrate B.P. with 125mg flucloxacillin as flucloxacillin sodium.
Magnapen Vials: Each vial contains 250mg ampicillin as Ampicillin Sodium B.P. with 250mg flucloxacillin as flucloxacillin sodium.
Uses: Severe infections. Post-operative chest and wound infections. Prophylaxis in major surgery.

Dosage: Adult: 1 capsule or 10ml syrup, or 1 vial qid. Children: 2-10 years, ½ adult dose. Under 2 years, ¼ adult dose. Ampiclox Neonatal (regd.) is recommended for the treatment of infections in neonates and premature babies. PL 0038/5001, 5009.
Contra-indications: Penicillin hypersensitivity, ocular administration.
Side-effects: As with other penicillins. An erythematous rash may occasionally occur, as with ampicillin. The incidence of this rash is particularly high in patients with infectious mononucleosis. If a rash is reported, it is advisable to discontinue treatment.
Pharmaceutical Precautions: Magnapen solutions for injection should be used immediately. Consult product literature before using with intravenous fluids.

Basic N.H.S. Prices: (correct at time of printing, Feb.79).
Capsules: 500mg, £18.06 (100 capsule pack).
Syrup: 250 mg per 5 ml, £3.18 (100ml).
Vials: 500mg, £7.45 (10 vials).

Magnapen is available to hospitals on regional contract dependent upon estimated usage.

Further information on Magnapen is available on request to the company.

Magnapen, BRL and the Company logo are registered trade marks.

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increase in cell membrane permeability with subsequent quantitative and qualitative changes in the normal distribution of extracellular and intracellular electrolytes is the initial change in the sequence of events that constitute the metabolic response to injury (Flear, 1973). This increase in cell membrane permeability was attributed to impaired tissue perfusion and hypoxia but the decrease in tissue oxygenation following routine surgery is comparatively small (Nunn, 1965). The changes in the extracellular fluid volume after surgery have been investigated in the past but the results have been contradictory (Flear, 1970). The substances used to measure extracellular fluid volume may enter the cells owing to a change in membrane permeability (Breckenridge et al., 1970) and give rise to erroneous conclusions. However, haemodilution was not the sole cause of postoperative hypophosphataemia as the extent of the reduction in serum inorganic phosphorus concentration, packed cell volume and serum albumin concentration showed quantitative differences. Nevertheless, the extent of the fall in serum inorganic phosphorus in the group receiving phosphorus supplementation does not suggest that deficient intake was a major factor. A further potential mechanism for loss of extracellular phosphorus is passage into the cell but this is most unlikely in this setting as all the evidence suggests that the opposite occurs following surgery (Cuthbertson, 1930).

It is concluded that the fall in the concentration of serum inorganic phosphorus following these elective operations was largely the result of haemodilution. However, the falls in concentration of serum inorganic phosphorus, and of red blood cell 2,3 diphosphoglycerate and adenosine triphosphate were small and self-correcting and there is no indication for routine postoperative phosphorus supplementation in uncomplicated elective surgery.

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References

BRECKENRIDGE I. M., DIGERNESS S. B. and KIRKLIN J. W. (1970) Distribution volume, equilibration time and exponential analysis of ^{82}Br after open intracardiac operations. *Ann. Surg.* **171**, 583–589.

CUTHBERTSON D. P. (1930) The disturbances of metabolism produced by bony and non-bony injury with notes on certain abnormal conditions. *Biochem. J.* **24**, 1245.

FLEAR C. T. G. (1970) Electrolyte and body water changes after trauma. *J. Clin. Pathol.* **23**, Suppl. 4 (*R. Coll. Pathol.*) pp. 16–31.

FLEAR C. T. G. (1973) Changes in extracellular fluid after trauma. *Proc. R. Soc. Med.* **66**, 23–26.

GROEN J., WILLEBRANDS A. F., KAMMINGA C. E. et al. (1952) Effects of glucose administration on the potassium and inorganic phosphate content of the blood serum and the electrocardiogram in normal individuals and in non-diabetic patients. *Acta Med. Scand*, **141**, 352–366.

GUILLOU P. J., MORGAN D. B. and HILL G. L. (1976) Hypophosphataemia: a complication of 'innocuous dextrose-saline'. *Lancet* **2**, 710–712.

JACOB H. S. and AMSDEN T. (1971) Acute hemolytic anemia with rigid red cells in hypophosphatemia. *N. Engl. J. Med.* **285**, 1446–1449.

KLOCK J. G., WILLIAMS H. E. and MENTZEN W. C. (1974) Hemolytic anemia and somatic cell dysfunction in severe hypophosphatemia. *Arch. Intern. Med.* **134**, 360–364.

LE QUESNE L. P. (1954) *Fluid Balance in Surgical Practice.* London, Lloyd-Luke, p. 290.

MAHONY J. F., HAYES J. M., INGHAM J. P. et al (1976) Hypophosphataemia osteomalacia in patients receiving haemodialysis. *Br. Med. J.* **2**, 142–144.

NUNN J. F. (1965) Influence of age and other factors on hypoxaemia in the postoperative period. *Lancet* **2**, 466–468.

RIEDLER G. F. and SCHEITLIN W. A. (1969) Hypophosphataemia in septicaemia: higher incidence in Gram-negative than in Gram-positive infections. *Br. Med. J.* **1**, 753–756.

ROWLANDS B. J. and GIDDINGS A. E. (1976) Postoperative hypophosphataemia. *Lancet* **2**, 1077.

TERRITO M. C. and TANAKA K. R. (1974) Hypophosphatemia in chronic alcoholism. *Arch. Intern. Med.* **134**, 445–447.

TRAVIS S. F., SUGERMAN H. J., RUBERG R. L. et al. (1971) Alterations of red cell glycolytic intermediates and oxygen transport as a consequence of hypophosphatemia in patients receiving hyperalimentation. *N. Engl. J. Med.* **285**, 763–768.

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The effect of aspirin on the fibrinolytic activity of gastric juice

T. E. O'BRIEN, HELEN HADLEY AND M. H. IRVING*

SUMMARY

Fibrinolytic activity in the gastric juice of normal subjects has been studied by a double-blind cross-over technique comparing the effect of placebo and pentagastrin against aspirin and pentagastrin. Aspirin effectively produced a gastritis and pure fibrinolytic activity was detected in the gastric juice, but the number of samples showing pure fibrinolytic activity did not differ between the two groups. In both the placebo and the aspirin groups the presence of a protease active at neutral pH and capable of dissolving fibrin is confirmed. Aspirin is unlikely to cause gastric bleeding by increasing local fibrinolytic activity within the stomach. The model, so constructed, is not sensitive enough to be of value in investigating further the role of gastric fibrinolytic activity in gastric haemorrhage.

FIBRINOLYTIC activators occur in many tissues (Astrup, 1966). Under normal circumstances the fibrinolytic system subserves the useful function of removing fibrinous deposits and maintaining the patency of small ducts and blood vessels. When such tissues are damaged, however, activation of the fibrinolytic system may potentiate bleeding, as has been demonstrated in the uterus and prostate (McNichol et al., 1961; Rybo, 1966).

Two studies (Cox et al., 1967; Nilsson et al., 1975) have implicated gastric fibrinolytic activity as an aetiological factor in gastroduodenal haemorrhage, and the results of two controlled trials in which an anti-fibrinolytic agent was used to treat patients with upper gastrointestinal haemorrhage would seem to confirm this (Cormack et al., 1973; Biggs et al., 1976). Gastric juice has been shown to be capable of dissolving fibrin and fibrin clots under certain circumstances (Oleson, 1972). This fact has obvious implications in patients who are actively bleeding from the stomach.

The aim of the present study was to ascertain whether it is possible to contruct a model in the human subject, to study fibrinolytic activity in gastric juice and to see whether increased local fibrinolysis might account for the known tendency for gastric bleeding to occur after the ingestion of salicylate.

Patients and methods

A double-blind cross-over study was performed on 10 healthy volunteer subjects who underwent two standard pentagastrin tests following the oral administration of aspirin and a placebo (lactose).

Capsules, containing 300 mg of either aspirin (acetylsalicylic acid) or lactose, were made by the hospital pharmacist. Six capsules were placed into each of two bottles labelled treatment A and treatment B. Only the pharmacist knew what each bottle contained. Cards giving instructions on the order in which the treatments were to be taken were placed in envelopes and randomly given to each subject. The volunteers were instructed to eat nothing after 12 midnight on the day of the test. At 12 midnight the volunteer swallowed three capsules as instructed on the card. The three remaining capsules were ingested 1–1½ h before the start of the pentagastrin test. Thus, a total of 1·8 g of compound was taken over a period of 8–9 h on an empty stomach. A standard pentagastrin test was then performed in the usual manner. The following samples of gastric juice were collected and examined for fibrinolytic activity: the resting gastric juice, basal samples taken at 30 min and 60 min; samples taken at 30 min and 60 min after the subcutaneous injection of pentagastrin (0·6 μg/kg).

The pH and the presence of blood and/or bile were noted on all the samples obtained.

After an interval of at least 2 weeks the test was repeated, the subject taking the remaining compound in a similar fashion.

Fibrinolytic activity in the gastric juice was assessed using a fibrin plate technique, the plates being prepared according to the methods of Astrup and Mullertz (1952) and Lassen (1953). In order to characterize the type of fibrinolytic activity obtained, plates were also prepared incorporating EACA and Trasylol.

The area of lysis obtained was determined by measuring the diameter of the lytic zone in two directions at right-angles to each other and multiplying the two measurements. An illuminated transparent plastic grid marked in 1-mm squares was used to facilitate the accurate measurement of the lytic area.

Fibrinogen from the same batch sample was used in the performance of all tests.

On completion of the study the code was broken and the results analysed.

Results

Ten subjects were studied, 5 male and 5 female, with a mean age of 28·9 years (range 20–42 years). Aspirin proved to be an effective gastric irritant, 40 per cent of the pre-pentagastrin and 53 per cent of the post-pentagastrin samples being frankly bloodstained, whereas after the placebo only 4 per cent of the pre-pentagastrin and 27 per cent of the post-pentagastrin samples were bloodstained.

Strict criteria have been adopted for defining pure fibrinolytic activity. Lysis occurring on standard and heated plates, but which was suppressed by EACA and Trasylol, was interpreted as pure fibrinolysis, except when the lysis on the heated plate was equal to or greater than that occurring on the standard plate. In this latter instance this was interpreted as non-specific proteolysis. Lysis occurring on all plates indicated non-specific proteolysis.

The patterns of activity obtained are shown in *Tables I* and *II*.

Pure fibrinolytic activity was seen in both groups, but there was no difference between the two groups in the numbers of samples showing this activity. Thus in the placebo group 6 out of 30 (20 per cent) of pre-pentagastrin samples and 4 out of 20 (20 per cent) post-pentagastrin samples showed pure activity, and in the aspirin group 7 out of 30 (23·3 per cent) pre-pentagastrin and 3 out of 20 (15 per cent) post-pentagastrin samples showed pure activity.

The patterns of lysis obtained in those samples showing pure fibrinolytic activity are shown in *Table III*. In addition, only 4 out of the 20 samples showing

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pure fibrinolytic activity were bloodstained. Also, of the 20 samples showing fibrinolytic activity, 13 had a gastric juice pH of 3·0 or less.

Discussion

It is a common clinical observation that in cases of upper gastrointestinal haemorrhage the bleeding is often intermittent in character. One possible explanation for this is a sequence of clot formation leading to cessation of bleeding, followed by spontaneous clot lysis leading to rebleeding. Several enzymes are capable of dissolving fibrin; among these are trypsin and other pancreatic proteases. Pepsin, in the presence of hydrochloric acid, has been shown to cause lysis of the fibrin in fibrin plates although pepsin alone is without effect (Cox et al., 1967). The demonstration by Nilsson (1975) of increased fibrinolytic activity in the gastric juice of patients bleeding from erosive gastroduodenitis, and their subsequent improvement following the administration of an antifibrinolytic agent, has important implications. The question this finding raises is: 'Would examination of the gastric juice of patients with upper gastrointestinal bleeding be of value in predicting which of these patients would benefit from anti-fibrinolytic therapy?' The present study has attempted to construct a model to investigate this possibility. The results show that in a certain proportion of cases gastric juice in normal subjects without gastric haemorrhage may exhibit pure fibrinolytic activity. The administration of a known gastric irritant, aspirin, did not increase the numbers of samples of gastric juice showing pure fibrinolytic activity.

Table I: PATTERNS OF LYSIS OBTAINED IN THE 10 SUBJECTS IN THE PLACEBO GROUP

	Pre-pentagastrin			Post-pentagastrin	
Subject	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
1	0	1	2	0	1
2	2	2	2	0	0
3	2	2	2	0	0
4	2	1	1	1	0
5	0	0	2	2	2
6	2	1	0	0	1
7	2	2	2	2	2
8	2	2	2	1	0
9	2	1	1	0	0
10	2	0	0	0	0

0, No lysis; 1, pure fibrinolysis; 2, non-specific proteolysis.

Table II: PATTERNS OF LYSIS OBTAINED IN THE 10 SUBJECTS IN THE ASPIRIN GROUP

	Pre-pentagastrin			Post-pentagastrin	
Subject	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
1	0	0	0	0	0
2	2	1	2	2	0
3	2	2	2	2	2
4	2	2	1	1	0
5	2	2	2	1	2
6	2	2	0	0	0
7	1	1	1	0	0
8	2	1	2	1	0
9	1	0	0	0	2
10	0	0	0	0	0

0, No lysis; 1, pure fibrinolysis, 2, non-specific proteolysis.

Table III: LYSIS AREA (mm^2) IN THOSE SAMPLES SHOWING PURE FIBRINOLYTIC ACTIVITY

Subject	Standard plate	Standard plate+EACA	Heated plate
1	40	—	—
2	72	—	50
3	120	—	—
4	143	—	—
5	249	—	58
6	70	—	—
7	150	—	—
8	20	—	—
9	70	—	—
10	90	—	48
11	48	—	—
12	80	—	—
13	169	—	50
14	154	—	121
15	49	—	—
16	361	—	100
17	56	—	—
18	374	—	144
19	64	—	—
20	49	—	—

Since the original report of Douthwaite and Lintott (1938), there has been increasing evidence to suggest an association between aspirin ingestion and the development of acute gastric mucosal lesions. The mechanisms of gastric haemorrhage after salicylate ingestion remain obscure. It is known, however, that aspirin ingestion causes exfoliation of gastric mucosal cells (Croft, 1963) and multiple erosions after repeated small doses (Croft and Wood, 1967). The amount of bleeding after aspirin ingestion is related to the particle size of the aspirin (Győry and Stiel, 1968), and in this study coarse aspirin (large particle size) was used. Aspirin is also known to affect platelet function, which may, of course, be relevant to any bleeding tendency (O'Brien, 1968). The occurrence of gastric bleeding is also related to gastric acidity—the higher the acidity the greater is the amount of bleeding (Davison et al., 1966; Croft and Wood, 1967)—and in this study the number of samples of gastric juice showing heavy bloodstaining increased after the administration of pentagastrin. As endoscopy was not performed on the subjects studied, it is not possible to be absolutely sure that the aspirin did in fact cause gastric erosions and a gastritis, and the evidence that this occurred rests only with the finding of increased numbers of samples of heavily bloodstained gastric juice in the aspirin-treated group. However, it is possible that this bloodstaining might simply reflect increased permeability of the gastric mucosa, as aspirin is known to cause changes in this (Smith et al., 1971). The purpose of administering pentagastrin was both to stimulate acid secretion, in the hope of enhancing the effect of the aspirin, and also to increase gastric mucosal blood flow (Thompson, 1969). Aspirin is known to effect changes in the fibrinolytic system of the blood (Menon, 1970; Moray, 1977), but the results in this study suggest that it does not alter fibrinolytic activity in gastric juice. The finding of 'pure' fibrinolytic activity in the gastric juice of normal subjects was surprising, as one would expect that any plasminogen activator present within the gastric lumen would be destroyed by gastric acid.

The most common action of gastric juice on fibrin plates is either no lysis at all or non-specific proteolysis. In this study the pH of the gastric juice was adjusted to 7·0 before the juice was placed on the plates. At this pH pepsin has no activity on fibrin plates; thus, the lysis obtained was probably not due to pepsin. In many samples showing large areas of non-specific proteolysis the juice was bile-stained, evidence of duodenal reflux. Almost certainly the lysis of fibrin in these samples was due to pancreatic proteases, although bile is known to contain activators of plasminogen (Oshiba et al., 1969). However, not all the samples causing proteolysis were bile-stained. Taylor (1959) has identified a protease in gastric mucosal tissue which is active at neutral pH and Eras et al. (1970), using histochemical techniques, also found proteolytic activity related to the epithelial surface of the gastric mucosa which was not inhibited by EACA or heat. The results of this study also serve to confirm the presence of an enzyme capable of dissolving fibrin which is active at pH 7·0. The origin of the fibrinolytic activity in the gastric juice remains open to conjecture. The studies of Cox et al. (1967, 1969) and of Thompson (1974) have demonstrated that the gastric venous blood may exhibit marked fibrinolytic activity. In our study the fibrinolytic activity demonstrated in the gastric juice in all but 7 of the samples was that of plasminogen activator. It is possible that the origin of this activator was the rich mucosal and submucosal capillary plexuses. However, the fibrinolytic activity in the gastric juice was not increased after inducing gastric hyperaemia with pentagastrin in either the aspirin or placebo groups. It is interesting to note also that the majority of the samples exhibiting pure fibrinolytic activity were not bloodstained, indicating that the presence of blood in the stomach is not necessarily associated with the findings of fibrinolytic activity in the gastric aspirate. The other possible source of the plasminogen activator activity is swallowed saliva, saliva having been shown to contain substantial amounts of plasminogen activator (Albrechtsen and Thaysen, 1955). The presence of an oral or nasogastric tube may induce the subject to swallow more frequently. It is of interest also to find that in 13 out of the 20 samples of gastric juice showing pure fibrinolytic activity the pH was 3·0 or less, showing that activator is not necessarily destroyed at once in an acid environment.

In conclusion, therefore, gastric juice may exhibit pure fibrinolytic activity in the absence of gastric bleeding. The administration of aspirin did not induce increased fibrinolytic activity in gastric juice even after giving pentagastrin, and this model so constructed is unlikely to be of use in the study of the fibrinolytic activity of gastric juice. The origin of the plasminogen activator present in the samples showing pure fibrinolytic activity remains open to doubt. However, the study does demonstrate that gastric juice is capable of dissolving fibrin even at neutral pH, and although this is not fibrinolysis in the accepted sense, it offers a possible explanation as to the cause of the intermittent nature of gastroduodenal haemorrhage.

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References

ALBRECHTSEN O. K. and THAYSEN J. H. (1955) Fibrinolytic activity in human saliva. *Acta Physiol. Scand.* **35**, 138–145.

ASTRUP T. (1966) Tissue activators of plasminogen. *Fed. Proc.* **25**, 42–51.

ASTRUP T. and MULLERTZ S. (1952) Fibrin plate method for estimating fibrinolytic activity. *Arch. Biochem.* **40**, 346–351.

BIGGS J. C., HUGH T. B. and DODDS A. J. (1976) Tranexamic acid and upper gastrointestinal haemorrhage: a double blind trial. *Gut*, **17**, 727–734.

CORMACK F., JOUHAR A. J., CHAKRABARTI R. R. et al. (1973) Tranexamic acid in upper gastrointestinal haemorrhage. *Lancet* **1**, 1207–1208.

COX H. T., POLLER L. and THOMPSON J. M. (1967) Gastric fibrinolysis: a possible aetiological link with peptic ulcer. *Lancet* **1**, 1300–1302.

COX H. T., POLLER L. and THOMPSON J. M. (1969) Evidence for the release of gastric fibrinolytic activity into peripheral blood. *Gut.* **10**, 404–407.

CROFT D. N. (1963) Aspirin and the exfoliation of gastric epithelial cells: cytological and biochemical observations. *Br. Med. J.* **2**, 897–901.

CROFT D. N. and WOOD P. H. N. (1967) Gastric mucosa and susceptibility to occult bleeding caused by aspirin. *Br. Med. J.* **1**, 137–141.

DAVISON C., HERTIG D. H. and DEVINE R. (1966) Gastric haemorrhage induced by non-narcotic analgesic agents in dogs. *Clin. Pharmacol. Ther.* **7**, 239–249.

DOUTHWAITE A. H. and LINTOTT G. A. M. (1938) Gastroscopic observations of the effect of aspirin and certain other substances on the stomach. *Lancet* **2**, 1222–1225.

ERAS P., HARPEL P. and WINAWER S. J. (1970) Histological localization of plasminogen activator and proteolytic activity in the human stomach and duodenum. *Gut* **11**, 851–854.

GYORY A. Z. and STIEL J. N. (1968) Effect of particle size on aspirin-induced gastrointestinal bleeding. *Lancet* **2**, 300–302.

LASSEN M. (1953) Heat denaturation of plasminogen in the fibrin plate method. *Acta Physiol. Scand.* **27**, 371–376.

MCNICHOL G. P., FLETCHER A. P., ALKJAERSIG N. et al. (1961) The use of epsilon-amino caproic acid, a potent inhibitor of fibrinolytic activity in the management of postoperative hematuria. *J. Urol.* **86**, 829–837.

MENON I. S. (1970) Aspirin and blood fibrinolysis. *Lancet* **1**, 364.

MORAY L. A. (1977) Increased blood fibrinolytic activity after aspirin ingestion. *N. Engl. J. Med.* **296**, 525–529.

NILSSON I. M., BERGENTZ S. E., WIKLANDER O. et al. (1975) Erosive haemorrhagic gastroduodenitis with fibrinolysis and low factor XIII. *Ann. Surg.* **182**, 677–682.

O'BRIEN J. R. (1968) Effects of salicylates on human platelets. *Lancet* **1**, 779–783.

OLESON E. S. (1972) Inhibition of gastric and duodenal proteases in the treatment of haemorrhage from peptic ulcer. 1. An experimental study of Bentonite and other protease inhibitors. *Scand. J. Gastroenterol.* **7**, 265–271.

OSHIBA S., HATA S. and OKAMOTO S. (1969) A plasminogen activator in mammalian bile. *Jap. J. Physiol.* **19**, 212–219.

RYBO G. (1966) Clinical and experimental studies on menstrual blood loss. *Acta Obstet. Gynecol. Scand.* **45**, Suppl. **7**, pp. 1–23.

SMITH B. M., SKILLMAN J. J., EDWARDS B. G. et al. (1971) Permeability of the human gastric mucosa. Alteration by acetylsalicylic acid and ethanol. *N. Engl. J. Med.* **285**, 716–721.

TAYLOR W. H. (1959) Studies on gastric proteolysis: proteinase activity of gastric juice and gastric mucosal extract at pH 6 to 8. *Biochem. J.* **71**, 626–632.

THOMPSON J. C. (1969) Gastrin and gastric secretion. *Ann. Rev. Med.* **20**, 291–314.

THOMPSON J. M. (1974) Fibrinolysis and the stomach: biochemical identification of the 'plasmin-like' enzyme. *Thromb. Diath. Haemorr.* (*Stuttg.*) **31**, 291–298.

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Technical index

Reagents

Thrombin: Bovine thrombin (Leo Laboratories) 5000 NIH units. 5 ml of N-saline and 5 ml of glycerol were added to each ampoule of thrombin, giving a concentration of 500 NIH units/ml. This was stored at −20 °C until ready for use. When ready, the thrombin solution was thawed and diluted 1 : 9 with 0·9 per cent NaCl giving a final concentration of 50 NIH units/ml.

Phosphate buffer: pH 7·3.

Epsilon-amino caproic acid: Epsikapron (AB Kabi, Stockholm). A 1 per cent solution was prepared in phosphate buffer.

Fibrinogen: Lyophilized fibrinogen (grade L) (AB Kabi, Stockholm). Reconstituted as a 1 per cent solution, divided into 2-ml aliquots and stored at −20 °C.

Streptokinase (AB Kabi, Stockholm). Supplied as lyophilized powder, 100 000 i.u. One vial (100 000 units) was dissolved in 50 ml 0·9 per cent NaCl, divided into 2-ml aliquots and stored at −20 °C until required.

Aprotinin: Trasylol, 1000 units/ml (Sigma).

The modified plates were prepared as follows:

EACA plate

8 ml of a 1 per cent solution of EACA in phosphate buffer were added to 2 ml of fibrinogen, the contents mixed and 9 ml of the mixture poured into the appropriate Petri dish. The solution was clotted with 0·1 ml thrombin (50 NIH units/ml).

Trasylol plate

6 ml of phosphate buffer and 2 ml of Trasylol (1000 units/ml) were added to 2 ml of fibrinogen, the contents mixed and 9 ml of the mixture poured into the Petri dishes. The solution was clotted with 0·1 ml thrombin.

0·03 ml of a solution containing 2000 units/ml of streptokinase were added to the heated plates as control.

Preparation of samples

After collection of the samples into small plastic containers, they were placed in a vacuum flask containing melting ice and transported to the laboratory without delay. The pH of each sample was adjusted to 7·0 and then 0 03 ml of the juice were immediately placed on the fibrin plates. The plates were then incubated for 18 h at 37 °C, after which time the areas of lysis obtained were measured using an illuminated transparent plastic grid.

Br. J. Surg. Vol. 66 (1979) 348–349

Chronic abdominal pain: a surgical or psychiatric symptom?

C. R. J. WOODHOUSE AND S. BOCKNER*

SUMMARY

A prospective investigation of chronic, non-specific abdominal pain in 20 patients is reported. The cause was found to be psychiatric in 8 (40 per cent), while a surgical cause was found in only 3 (15 per cent). Four had irritable colon (20 per cent) and no diagnosis was made in 5 (25 per cent). It is suggested that such pain is more often a psychiatric than a surgical symptom and therefore a psychiatric consultation should be a routine part of the investigation.

CHRONIC abdominal pain is one of the commoner presenting symptoms in surgical outpatient clinics. In many cases the pain is non-specific, the history does not suggest disease in any particular organ and physical signs are few or absent. Extensive investigation fails to show a surgical cause and the patients often remain undiagnosed. We have used a combined surgical and psychiatric approach to try to establish a diagnosis in a group of such patients.

Patients and methods

We investigated all patients over 18 years of age presenting with a history of abdominal pain for more than 2 years and whose symptoms did not indicate a specific disease. A full history was taken with particular reference to the duration of the pain, periodicity, precipitating factors and associated symptoms. They were specifically asked about recurrent pains in childhood and at other times. If they had had abdominal or pelvic surgery the indications for it were established.

All had a 'ward test' of urine (Haemocombistix, Ames Ltd), urine culture and a full blood count. Other investigations were carried out according to the clinical indications (investigations are shown in *Table I*). If there was no somatic diagnosis, a full psychiatric assessment was made.

Results

Twenty-eight patients were seen between April and December 1977. Eight failed to complete the course of investigation and were lost to follow-up. Twenty patients are available for analysis. A definite diagnosis was made in 15 patients: 3 had a 'surgical' disease, 8 a psychiatric disease and 4 had an irritable colon. In the remaining 5 patients no diagnosis was made. The results are summarized in *Table II*.

Surgical causes

There were 3 patients in this group (15 per cent). All were over 60 years old. Their symptoms were not typical of their disease, but were relieved by conventional treatment for the identified lesion. The first patient was a woman of 76 years with a long history of pain in the epigastrium and both iliac fossas. She was eventually found to have diverticulosis coli with an irregular stricture of the upper sigmoid. At operation the stricture was found to be due to inflammatory changes in the bowel wall. Reilly's myotomy was performed and she remains free of symptoms 14 months later.

The second patient was correctly diagnosed as having gallstones only when seen during an attack of acute cholecystitis. The third woman had longstanding collapse of 3 thoracic vertebrae causing root pain, which was only diagnosed, after prolonged investigation, when the crucial past history was elicited.

Psychiatric causes

A psychiatric diagnosis was made in 8 cases (40 per cent). Five had chronic anxiety states, 2 had obsessional states and 1 had endogenous depression.

There were 6 women and 2 men in this group, with an average age of 32 years (range 25–44). Pain had been present for between 2 and 17 years but 3 patients could give no definite duration. None remembered having pain before puberty. All were vague about

Table I: INVESTIGATIONS UNDERTAKEN IN 20 PATIENTS WITH CHRONIC, NON-SPECIFIC ABDOMINAL PAIN

Investigation	No. of cases
Barium enema and sigmoidoscopy	16
Barium meal	15
Intravenous urogram	13
Oral cholecystogram	8
Liver function tests	3
Thyroid function tests	2
Spinal X-rays	2
Intravenous cholangiogram	1
Serum amylase	1
Lactose tolerance test	1

Table II: DIAGNOSIS OF 20 PATIENTS WITH CHRONIC, NON-SPECIFIC ABDOMINAL PAIN

Diagnosis	No. of cases	
Surgical causes	3	
Inflammatory stricture of colon		1
Gallstones		1
Collapsed thoracic vertebrae		1
Psychiatric causes	8	
Chronic anxiety states		5
Obsessional states		2
Endogenous depression		1
Irritable colon	4	
Undiagnosed	5	

Table III: SYMPTOMS ASSOCIATED WITH ABDOMINAL PAIN IN 8 PSYCHIATRIC CASES

Symptom	No. of cases
Bowel disturbance	3*
Worsening of pain with stress	3
Anorexia	2
Abdominal swelling	2
Vomiting	2
Weight loss (only during pain)	1
Nausea	1
Dyspareunia	1
Micturition disturbance	1

* Only occasionally in 1 case.

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their symptoms, admitting, for example, to intermittent pain, yet only 2 having an accurate idea of its periodicity. Associated symptoms were scarce, as *Table III* shows.

Physical signs were unhelpful. The patients all looked well and none was obese. Four had tenderness in the right iliac fossa, 2 with a poorly defined mass (these 2 were submitted to elective appendicectomy, 1 was unchanged after the operation and 1 was worse). Further consultation eventually established the correct diagnosis.

Conventional treatment was given using psychotherapy and drugs as required; 5 out of the 8 have improved and have had no recurrence of their pain. The follow-up of these patients now ranges between 8 and 15 months and none has developed an organic disease.

Irritable colon

In 4 patients (20 per cent) a diagnosis of irritable colon was made. All had lower abdominal pain with alteration of bowel habit; 3 had constipation and 1 had variable constipation and diarrhoea. In spite of at least 3 years of history, all remained in good general health without weight loss. Only 1 patient associated his pain with stress and none had distinct psychiatric disease.

Two patients had tender descending colons and 1 had minimal reddening of the rectal mucosa, which was found to be normal on histology of multiple biopsies. All 4 had normal barium enema examinations and extensive investigation failed to show another cause for the symptoms. The patients were treated with bulk laxative (ispaghula husk) with complete relief of symptoms and they all remain well after 11–15 months' follow-up.

Undiagnosed group

In 2 men, aged 53 and 54 years respectively, the symptoms were considered sufficiently severe to warrant laparotomy: no pathology was found, but 1 had a normal appendix removed. Both remain free of abdominal pain after 8 and 14 months of follow-up. Three other patients remain undiagnosed and continue to have pain.

Discussion

Chronic non-specific abdominal pain is a notoriously difficult symptom to diagnose. In one retrospective review of patients whose pain 'failed to conform to specific patterns' only 10 of 76 were diagnosed. The younger the patient and the greater the duration of symptoms, the more unlikely diagnosis became (Sarfeh, 1976). Gynaecological practice reveals similar experience when only 14 out of 49 patients with pain of 'chronic non-specific type' were found to have an abnormality on laparoscopy (Ferguson, 1974). Even in acute episodes of abdominal pain diagnosis has been shown to be possible in less than half of 1000 cases (Brewer et al., 1976).

Abdominal pain has been known as a symptom of emotional disorders since ancient Greek times; hence the term 'hypochondriasis', meaning 'below the costal cartilages', coined by Hippocrates. In the language of symptoms, the unhappy patient is literally 'bellyaching' about his problems. Anxiety states, obsessional states and endogenous depressions are the commonest psychiatric causes for abdominal pain (Gomez and Dally, 1977). Recently the role of psychiatric factors in the aetiology of chronic abdominal pain has been neglected, though such factors are well established in children (Apley and Naish, 1958; Dodge, 1976). Although it has been suggested that little bellyachers grow up into big bellyachers (Editorial, 1975), such histories were not given by our patients.

In 8 of our 20 patients (40 per cent) psychiatric causes for chronic abdominal pain were found and over half of them have made a good response to treatment. A further 4 had irritable colon, and it has been shown that in this condition disturbed colonic motility can be mediated by emotional upsets (Chaudhary and Truelove, 1961). The histories of our patients were as long as 17 years, and yet their general health remained good. Nevertheless, there is a clear possibility that they may yet develop an organic disease, and a change of symptoms or relapse while under psychiatric treatment would be an indication for further investigation.

Only rarely did we find that this type of pain had a 'surgical' cause and only when the patient was over 60 years old. We now accept that where a patient is under 40 years old, has few symptoms other than pain and no physical signs, it is sufficient to test the urine, do a full blood count and one radiological investigation. Within this framework the patient is shown that his complaint is being taken seriously and a psychiatric consultation is accepted. In this series no organic diagnosis would have been missed with this programme. We regard the psychiatric assessment as part of the routine work-up and positive psychiatric features do not preclude further investigation.

Our experience with this difficult group of patients is that diagnosis is possible in 75 per cent of cases. Chronic, non-specific abdominal pain is more often a psychiatric than a surgical symptom and a combined approach by both specialties is helpful.

Acknowledgement

We are most grateful to Mr J. M. Beaugie for permission to report on his patients.

References

APLEY J. and NAISH N. (1958) Recurrent abdominal pains: a field survey of 1000 school children. *Arch. Dis. Child.* **33**, 165–170.

BREWER R. J., GOLDEN G. T., HITCH D. C. et al. (1976) An analysis of 1000 consecutive cases of abdominal pain in a university hospital emergency room. *Am. J. Surg.* **131**, 219–223.

CHAUDHARY N. A. and TRUELOVE S. C. (1961) Human colonic moility. *Gastroenterology* **40**, 27–36.

DODGE J. A. (1976) Recurrent abdominal pain in children. *Br. Med. J.* **1**, 385–387.

EDITORIAL (1975) Do little bellyachers become big bellyachers? *Br. Med. J.* **2**, 459.

FERGUSON I. L. C. (1974) Laparoscopy for the diagnosis of non-specific lower abdominal pain. *Br. J. Clin. Pract.* **28**, 163–165.

GOMEZ J. and DALLY P. (1977) Psychologically mediated abdominal pain in surgical and medical outpatient clinics. *Br. Med. J.* **1**, 1451–1453.

SARFEH I. J. (1976) Abdominal pain of unknown aetiology. *Am. J. Surg.* **132**, 22–25.

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Interstitial emphysema of the stomach

A. R. TURNBULL AND R. C. MICHELL*

SUMMARY

A case of interstitial emphysema of the stomach is reported and the possible aetiological factors involved are discussed.

THE presence of gas within the wall of the stomach is rare and probably unfamiliar to many surgeons. The condition may occur as a result of a phlegmonous gastritis due to gas-forming organisms, but it may also occur in non-infective conditions.

Case report

An 85-year-old diabetic woman presented as an emergency with a 1-week history of epigastric pain and vomiting. Two months previously she had been admitted with a haematemesis and melaena, and a barium meal examination had shown a duodenal ulcer with pyloric narrowing. On that occasion she had been treated conservatively with cimetidine and her condition had improved sufficiently to allow her to undergo a total hip replacement. However, a week following this procedure she had developed epigastric pain which radiated retrosternally. This had been associated with profuse vomiting and she had had further melaena. On this present admission the patient was clinically dehydrated but the temperature was normal, the pulse rate was 84/min and she was normotensive. There was epigastric tenderness and a succussion splash could be elicited. Investigations showed a haemoglobin of 15·8 g/dl and a white blood cell count of $24{\cdot}4\times10^9$/l. The blood urea was 28·0 mmol/l and the sodium was 119 mmol/l, potassium 3·8 mmol/l and bicarbonate 33 mmol/l. The blood glucose was 14·0 mmol/l. Abdominal radiographs (*Fig.* 1) showed a large stomach outlined by a linear gas shadow. The patient was rehydrated and her biochemistry corrected. Gastric lavage was carried out and she came to laparotomy 2 days later. At operation she was found to have a large stomach with pyloric stenosis secondary to duodenal ulceration. Gallstones were also present. There was crepitus of the stomach wall similar to subcutaneous surgical emphysema. A truncal vagotomy and Heineke–Mickulicz pyloroplasty was performed and the gallbladder removed. The cut surface of the stomach appeared normal macroscopically and there was no evidence of inflammation. The patient made a satisfactory postoperative recovery from this procedure, and has remained well since.

Discussion

Gas may be seen in the wall of a hollow viscus, such as the stomach, in various situations: these have been classified into three groups by Colquohoun (1965). It may result from infection with gas-forming organisms, it may occur in cystic pneumatosis intestinalis and it may present as interstitial emphysema associated with outlet obstruction.

When the condition is due to infection with gas-forming organisms it is known as emphysematous gastritis. This has been reported following the ingestion of corrosives, gastric infarction or gastroduodenal surgery (Meyers and Parker, 1967). The patient becomes extremely ill with signs of overwhelming infection and surgery has little effect on the outcome, which is invariably fatal. Abdominal radiographs show a contracted stomach with numerous small gas bubbles within the wall.

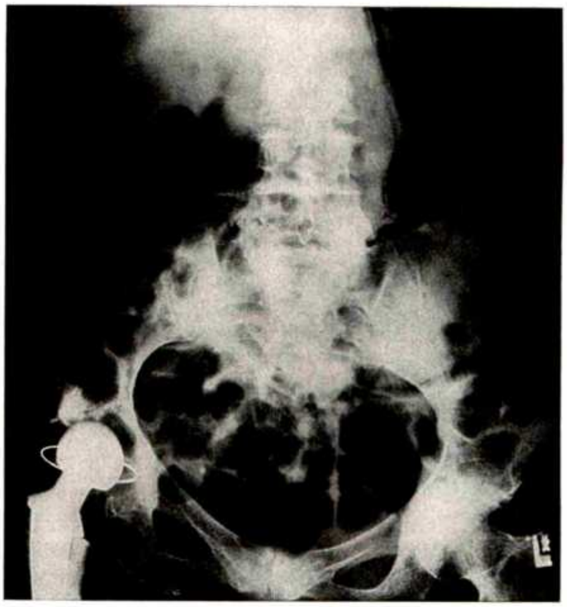

Fig. 1. Plain abdominal radiograph showing a large stomach outlined by a linear gas shadow.

Cystic pneumatosis intestinalis is more commonly seen in the colon and rarely affects the stomach. However, it has been described in patients with chronic pulmonary disease and pyloric obstruction (Colquohoun, 1965). The radiographic appearances are similar to those of emphysematous gastritis, but the stomach is not contracted. The two conditions can be differentiated clinically.

Interstitial emphysema of the stomach is associated with outlet obstruction and has been described secondary to duodenal obstruction from impacted gallstones (Schorr and Marcus, 1962), and secondary to carcinoma of the pyloric antrum (Ward, 1960). The condition may result from raised intraluminal pressure caused by vomiting. In this condition the abdominal radiograph shows an overdistended stomach outlined by a submucosal gas shadow or stripe.

The clinical picture and radiographic appearances in the case described here are those of interstitial emphysema of the stomach secondary to pyloric stenosis from duodenal ulceration. Although the white blood cell count was significantly raised preoperatively, there was no evidence of a severe or overwhelming infection to suggest that the patient had emphysematous gastritis. At operation there was no sign of an inflammatory process, but in retrospect it would have been of interest to have taken swabs for bacterial examination and a biopsy of the stomach wall for histology. In addition, the outcome was favourable, whereas emphysematous gastritis is invariably fatal. Cystic pneumatosis intestinalis has

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been described with pyloric obstruction but the radiographs of the patient showed an overdistended stomach outlined by a linear gas shadow or stripe. This is the characteristic appearance of interstitial emphysema rather than cystic pneumatosis, where there are numerous gas bubbles within the wall of the viscus.

Acknowledgements

We are grateful to Mr A. P. Ross for permission to report this case and to Mrs C. Bright for typing the manuscript.

References

COLQUOHOUN J. (1965) Intramural gas in hollow viscera. *Clin. Radiol.* **16**, 71–86.

MEYERS H. I. and PARKER J. J. (1967) Emphysematous gastritis. *Radiology* **89**, 426–431.

SCHORR S. and MARCUS M. (1962) Intramural gastric emphysema. *Br. J. Radiol.* **35**, 641–644.

WARD P. R. (1960) Interstitial gastric emphysema. *Br. J. Radiol.* **33**, 458–459.

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Surgical Research Society

The Winter Meeting of the Surgical Research Society was held at the Royal Free Hospital and Medical School on 4 and 5 January 1979 with Professor R. B. Duthie (President of the Surgical Research Society) in the chair. The following papers were presented.

1. Intravenous feeding in cancer patients receiving radiotherapy

D. VALERIO, A. MALCOLM and G. L. BLACKBURN, *Nutrition Metabolic Clinic, Cancer Research Institute, New England Deaconess Hospital, Boston, Massachusetts*

Malnutrition is a common feature of cancer (Schein et al., 1975) while intravenous feeding has been proposed as a significant support to cancer therapy (Copeland et al., 1977). A randomized prospective trial was designed to investigate the role of intravenous feeding in patients, who were planned to receive 4000 rad minimum to the abdomen or pelvis. Twenty patients entered the study: 11 were randomized to intravenous feeding receiving 40–45 kcal kg^{-1} d^{-1}, and 9 control subjects were allowed to eat normally. A nutritional assessment was made before and at the end of radiotherapy, with measurement of triceps skinfold, arm muscle circumference, creatinine height index, albumin, transferrin, lymphocyte count, reticulocyte count and delayed hypersensitivity skin testing.

The patients receiving intravenous feeding had more advanced cancer, a lower initial serum albumin and a greater pre-treatment weight loss than the controls. In the group receiving feeding an average weight gain of 2·1 kg occurred ($P<0{\cdot}05$) while the controls maintained their weight. Albumin levels fell in both groups, while a significant rise in transferrin level ($P<0{\cdot}01$) and reticulocyte count ($P<0{\cdot}01$) occurred in the feeding group and transferrin levels fell in the control group. In the feeding group 5 patients had a 50 per cent or more reduction in tumour mass compared with 3 in the control group. The catheter-related sepsis rate was zero.

These preliminary data suggest that intravenous feeding may play an important supportive role and may be given safely to the nutrionally depleted cancer host.

COPELAND E. M., DALY J. M. and DUDRICK S. J. (1977) Nutrition as an adjunct to cancer treatment in the adult. *Cancer Res.* 37, 2451–2456.

SCHEIN P. S., MACDONALD J. S., WATERS C. et al. (1975) Nutritional complications of cancer and its treatment. *Semin. Oncol.* 2, 337–347.

2. The continent ileostomy reservoir: a comparative study of the competence of five valve designs

B. CRANLEY and S. T. D. MCKELVEY, *Department of Surgery, Queen's University, Belfast*

Valve extrusion is one of the most troublesome problems associated with the continent ileostomy reservoir (Goligher and Lintott, 1975). We have investigated the competence of three valves in current clinical use and have included two of our own modifications for comparison as follows:

I. Kock valve with serosal diathermy ($n=6$).

II. Kock valve with seromuscular diathermy (Madigan, 1976) ($n=6$).

III. Kock valve with offsetting of the two mesenteric leaves to allow suturing between them (Kock, 1976) ($n=6$).

IV. The gut is transected. A nipple is fashioned in the distal segment and reinserted into the proximal segment ($n=6$).

V. Kock valve with mesentery excluded from the intussusception ($n=5$).

Each valve was made in an isolated loop of dog's ileum. After 10 weeks all valves were subjected to incremental pressures and leakage pressure was recorded.

The performance of types II, III, IV and V was compared with that of the standard valve (type I) (Table).

Statistically significant differences in performance were observed between type I and the other valves. Seromuscular diathermy and offsetting the mesentery improves valve function. Excluding mesentery from the intussusception prevents extrusion at the mesenteric aspect without producing ischaemia. This design merits further investigation.

	Leakage pressure (mmHg)				
	I	II	III	IV	V
	0	60	100	170	185
	0	0	140	80	20
	10	60	40	40	250
	0	26	74	0	10
	0	10	100	70	10
	0	80	94	40	—
Mean	1·67	39·33	91·33	66·67	95·00
P		$<0{\cdot}02$	$<0{\cdot}01$	$<0{\cdot}01$	$<0{\cdot}01$

Statistical tests: Kauskar–Wallis analysis of variance and Mann–Whitney U test.

GOLIGHER J. C. and LINTOTT D. (1975) Experience with 26 reservoir ileostomies. *Br. J. Surg.* 62, 893–900.

KOCK N. G. (1976) Symposium: Present status of the continent ileostomy: surgical revision of the malfunctioning ileostomy. *Dis. Colon Rectum* 19, 200–206.

MADIGAN M. R. (1976) The continent ileostomy and the isolated ileal bladder. *Ann. R. Coll. Surg. Engl.* 58, 62–69

3. Results of conservative management of patients with acute traumatic intradural haematomas

S. GALBRAITH, G. TEASDALE and B. JENNETT, *Department of Neurosurgery, Institute of Neurological Sciences, Glasgow*

Since the introduction of the CT scanner it has become apparent that intracranial haematomas can be present in the absence of clinical deterioration and in situations in which previously they would not have been suspected. Because the natural history of these haematomas was not known, we have investigated how often surgery was required and whether or not this could be predicted.

Eighteen patients with an acute traumatic intradural haematoma demonstrated by CT scanning and in whom there was no neurological deterioration were investigated. Patients were closely observed and intracranial pressure was monitored with an intraventricular catheter. Surgery was performed if there was clinical deterioration or if there was no improvement.

Seven patients required an operation and, of these, 4 made a good recovery, but 3 died. Of those managed without an operation, 10 made a good recovery and 1 remains severely disabled. Patients who were not in a coma and had no midline shift did not require surgery. However, apart from this, age, midline shift, intracranial pressure and level of responsiveness were unhelpful in predicting the need for surgery.

In this series only 39 per cent of patients eventually required an operation. Yet, because of the lack of certainty of their clinical course, and the difficulties encountered in adopting a conservative approach, we currently advise surgery in all patients except those with no midline shift and who are not in a coma.

4. The surface ultrastructure of normal and ectatic human breast ducts

R. E. MANSEL and L. E. HUGHES, *University Department of Surgery, Welsh National School of Medicine, Cardiff*

The detailed surface anatomy of human subareolar breast ducts has been examined in a scanning electron microscope and correlated with the light microscopy appearances of adjacent sections. Normal ducts, obtained from 10 young, asymptomatic women undergoing reduction mammoplasty, were shown to possess numerous longitudinal folds and at high power the apices of the individual ductal cells were easily seen. Apocrine metaplasia was commonly present in these 'normal' ducts and appeared to be due to protrusion of the apices of the ductal cells.

A second group of dilated ducts obtained from 14 women undergoing duct resection for mammary duct ectasia was examined and compared with the 'normal' ducts. The surface ultrastructure of these ducts differed from normal in three respects: the longitudinal folds were flattened or absent, apocrine metaplasia was generally absent and the duct cells possessed smaller and less numerous surface microvilli. Ducts removed for inflammatory duct ectasia were lined by a 'carpet' of inflammatory cells lying on an intact epithelial surface. These observations lend support to the hypothesis (Bonser et al., 1961) that the primary defect of mammary duct ectasia is ductal inflammation, and that the dilatation is secondary to atrophy consequent upon the inflammation.

BONSER G. M., DOSSET J. A. and JULL J. W. (1961) *Human and Experimental Breast Cancer*. London, Pitman Medical, pp. 237–265.

5. Macrophage/monocyte function in cancer patients

W. CANDLISH and J. BANCEWICZ, *Department of Surgery, Western Infirmary, Glasgow*

Macrophage/monocyte function may be important in cancer (Lauder, 1977), but there are few tests for clinical use. We have evaluated a new test that may measure phagocytosis of tumour cells (Halloran and Stylianos, 1978).

Antibody-coated tumour cells incubated with macrophages become resistant to lysis by complement. The degree of abrogation of complement lysis (ACL) may measure phagocytosis of the target cells. Mouse peritoneal exudate cells produced marked ACL (56·6±8·2 per cent) in a xenogeneic system. Effector cells adhered to plastic and were more efficient when activated by monolayer culture for 24 h. ACL did not occur at 4 °C and is therefore not simply a measure of binding to Fc receptors. Microscopic studies showed evidence of phagocytosis of tumour cells by macrophages in monolayer culture.

Peripheral blood mononuclear cells were obtained from human subjects by density gradient centrifugation. Adherent cells, after monolayer culture for 24 h, demonstrated ACL of xenogeneic tumour cells. Cryopreserved cells maintained their ability to mediate ACL.

In a small pilot study cryopreserved mononuclear cells from 3 healthy subjects and 6 patients with advanced cancer all demonstrated ACL of similar magnitude.

HALLORAN P. F. and STYLIANOS S. K. (1978) Macrophage–alloantibody: target cell interactions. *Transplantation* 25, 296–301.

LAUDER I. (1977) In: JAMES K., MCBRIDGE B. and STUART A. (ed.) *The Macrophage and Cancer*. Edinburgh, Macrophage and Cancer Editors, pp. 411–417.

6. Surgical decision-making

C. V. RUCKLEY, J. B. P. FERGUSON, CONSTANCE CUTHBERTSON and DOROTHY LEIGHTON, *General Surgical Unit, Western General Hospital, Edinburgh*

When alternative levels of surgical care are available (e.g. minor outpatients, major day care, 5-day and main ward) the efficient use of resources necessitates accurate selection of patients in the outpatient clinic.

Health Service statistics are available concerning inpatients but there is no corresponding audit of outpatient clinics or operations. We have studied the decision-making process prospectively by analysing the entire hospital course of 2000 consecutive patients. The surgeon, when putting a patient on the waiting list, was asked to select the simplest grade consistent with satisfactory care, to forecast the duration of stay and to record the factors influencing the decision.

A total of 1049 patients (52 per cent) was put on the waiting list over a 10-month period: minor 361 (34 per cent), day care 87 (8 per cent), 5-day 315 (30 per cent), main ward 286 (28 per cent). To date, 666 have completed their hospital course and clinic follow-up. The main factor influencing the decision on choice of level was medical in 88 per cent, social 3 per cent, psychological 1 per cent, mixed 8 per cent. The selection of the level of care was accurate in that only 10 (1·5 per cent) had to be transferred to a level of care other than that chosen while 14 (2 per cent) had to be readmitted. The forecast of duration of postoperative stay was correct to the nearest day in 37 per cent, underestimated in 23 per cent and overestimated in 40 per cent.

We conclude that for a given surgical population it is possible to calculate quite precisely the scale of the various levels of care required. Forecasting of outcome can be sufficiently accurate to allow better use of surgical resources.

7. The appearance of endotoxin following urethral instrumentation

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'Catheter fever' has been recognized as a complication of urethral instrumentation for many years (Mitchell et al., 1962). In an attempt to elucidate further the mechanism of this phenomenon we have studied 10 patients undergoing urethral instrumentation (9 cystoscopies and 1 urethral dilatation). Venous blood samples were taken before instrumentation, immediately after, half an hour after and hourly for 5 h. The samples were assayed for endotoxin using the Limulus amoebocyte lysate test, and cultured both aerobically and anaerobically. Before instrumentation mid-stream specimens of urine (MSSU) and urethral swabs were taken.

All patients were Limulus test negative (no endotoxin detected) before instrumentation. Immediately after 9 out of 10 were Limulus test positive (endotoxin detected) and the tenth was positive after an hour. Only 1 patient was Limulus test positive at 2½ h, but 6 out of 10 were positive at between 3½ and 5½ h. All blood cultures ($n = 80$) were sterile. Organisms were cultured from one MSSU and one urethral swab.

We have demonstrated that urethral instrumentation is associated with the appearance of endotoxin in the bloodstream and also that in some patients endotoxin reappears at a time when catheter fever characteristically occurs.

MITCHELL J. P., SLADE N. and LINTON K. B. (1962) Instrumental bacteraemia and its prevention. *Br. J. Urol.* 34, 454–458.

8. Management of postoperative pain

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Reports (Fry, 1976; Leading Article, 1976) have suggested better control of postoperative pain by continuous opiate than by intramuscular administration. We undertook a double-blind trial to compare the two methods.

Forty-five patients with vertical abdominal incisions were given, after recovery of consciousness, a slow intravenous injection of morphine sulphate to a dose which relieved pain without overt respiratory depression. Over 72 h, and by random allocation, patients then received: 3·5 times the dose by continuous i.v. infusion (A); 12 times the dose by i.m. injection first 4-hourly and then 6-hourly (B_1); p.r.n. injections of the dose (B_2). Blinding between A and B_1 was achieved by i.m. or i.v. saline respectively; B_2 also received saline i.v. Subjects completed a linear analogue 12-hourly on their pain experience for the period. Vital capacity (VC) and peak expiratory flow rate (PEFR) were measured 12-hourly.

There was alway a significant difference (1 per cent, Mann–Whitney U test) on the analogue scale in favour of A against B_2. B_1 were intermediate between p.r.n. and i.v. but could not be statistically separated from either. VC and PEFR showed similar patterns.

	Hours postop.		
	24	48	72
Peak flow			
A	34	40	50
B_1	38	48	74*
B_2	46*	56*	63
Vital capacity			
A	28	37	50
B_1	33	41	53
B_2	42*	51*	60*

% of preoperative values (means).

* $P<0·05$ compared to A (Mann–Whitney U test).

Continuous i.v. infusion is the method of choice for postoperative pain relief with a minimum dose of opiate.

FRY E. M. (1976) Postoperative pain. *Br. Med. J.* **2**, 817.
LEADING ARTICLE (1976) *Br. Med. J.* **2**, 664.

9. A comparison of pyloroplasty and pyloric ring dilatation as a drainage procedure for truncal vagotomy

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Forcible stretching (S) of the pylorus as an accompaniment to truncal vagotomy (TV) does not result in gastric stasis (Longrigg and Pringle, 1978). In view of the theoretical advantages of TV+S over TV+P (pyloroplasty), the present study was devised to compare these two operations.

Twenty-five patients with chronic duodenal ulceration had their liquid gastric emptying estimated after drinking 300 ml 15 per cent dextrose solution labelled with ^{99}Tc^{m} sulphur colloid. They were randomly allocated to either the TV+S (13) or TV+P (12) operation. Six months postoperatively the test was repeated and a clinical assessment made using a modified Visick grading.

The percentage emptying of dextrose solution at 5-min intervals was determined for each patient. The difference (D) between values for pre- and postoperative emptying was calculated for each interval, thus allowing a comparison to be made between the two operations using *t* test analysis. A greater value for D denotes increased emptying and, as can be seen in *Table I*, during the first 10 min the TV+S group empty at a significantly ($P<0·01$) slower rate than the TV+P group. This trend continues throughout the first hour.

Table I: DIFFERENCE BETWEEN PERCENTAGE OF MEAL REMAINING IN THE STOMACH PRE- AND POSTOPERATIVELY

Min. after drinking	TV+P	TV+S
5	42±5·9	15±3·4
10	51±5·8	35±9·7
25	42±2·8	29±7·9
45	30±3·9	20±4·3
65	21±4·7	3±8·5

All results are mean±s.e. mean.

Considering the overall clinical results (*Table II*), it is clear that as yet no obvious difference exists between the two operations.

Table II: VISICK GRADING OF FUNCTIONAL RESULTS 6 MONTHS AFTER OPERATION

	Visick grade			
	I	II	III	IV
TV+P	4	7	1	0
TV+S	6	5	2	0

In conclusion, the rapid gastric emptying of a liquid meal seen after TV+P is far less pronounced following TV+S, especially in the first 10 min. However, the clinical assessment at 6 months shows no obvious difference between the two operations.

LONGRIGG N. and PRINGLE R. (1978) A new method of gastric drainage following truncal vagotomy. *Arch. Surg.* **113**, 905–906.

10. Effects of somatostatin in duodenal reflux and the control state

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Dogs with surgically produced duodenal reflux hypersecrete acid in response to pentagastrin, although the response to histamine is identical to the control response (Thomas, 1978). One explanation for this hypersecretion could be suppression of an inhibitory mechanism active against gastrin, but not to histamine. The effects of somatostatin were, therefore, studied in both dogs with duodenal reflux and control dogs.

Dose–response curves to an intravenous infusion of somatostatin were constructed using doses of 0·25, 0·5, 1·0, 2·0, 4·0 and 8·0 μg kg^{-1}h^{-1} with maximal background stimulation using pentagastrin 8·0 μg kg^{-1}h^{-1} or histamine 80 μg kg^{-1}h^{-}h^{1}. With 0·25 μg kg^{-1}h^{-1} of somatostatin, mean inhibition of pentagastrin-stimulated gastrin acid secretion was 54·6 per cent in the control group, but only 30·3 per cent in the reflux group ($0·02>P>0.01$ Mann–Witney U test), while at higher doses there was no significant difference. With histamine-stimulated gastric acid secretion the threshold dose of somatostatin for inhibition was 1·0 μg kg^{-1}h^{-1} with no significant difference between the two groups.

Dose–response curves to pentagastrin with a continuous infusion of 0·25 μg kg^{-1}h^{-1} somatostatin in dogs with duodenal reflux produced identical responses to those seen in control dogs with pentagastrin alone, thus abolishing the hypersecretion seen in the reflux group with pentagastrin alone. These results are consistent with somatostatin playing a role in an inhibitory mechanism that is suppressed in alkaline reflux.

THOMAS W. E. G. (1978) Gastric acid secretion studies in response to pentagastrin in duodenal reflux and bile diversion. *J. Physiol.* **281**, 36–37*P*.

11. Further studies on gastric fundic factor

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Recent studies (Elder and Lomas, 1977) have provided evidence for the release of a humoral substance from gastric fundic mucosa after alkalinization of the lumen. This factor was shown to reduce the absorption of the tracer ion ^{99}Tc^{m} and of glucose from the antrum in rabbits and conscious dogs. In order to investigate this phenomenon further, a rat bioassay was developed using ^{99}Tc^{m} in the antral or jejunal lumen, the absorption of tracer being monitored by counting samples of peripheral venous blood at 5-min intervals.

Intravenous infusion of a neutral gastric fundic extract or stimulation of the fundas by distension with air or stimulation by exposure to alkaline buffer (pH 8) all depressed the absorption of the tracer ion from the antrum (80 per cent reduction, $P<0·01$) and to a lesser extent from the jejunum (15–50 per cent reduction, $P<0·05$).

The effects are not reproduced by i.v. histamine (0 005 μg kg^{-1} min^{-1}), and do not appear to be due to a change in mucosal blood flow as measured by Sapirstein's method (Sapirstein, 1958).

Preliminary biochemical data indicate that the biological activity of the neutral fundic extract resides in a heat-stable, dialysable, small protein fraction with a molecular weight <10 000.

ELDER J. B. and LOMAS J. (1977) Humoral inhibition of antral absorption of glucose and ^{99}Tc^{m}. *Br. J. Surg.* **64**, 824.
SAPIRSTEIN L. A. (1958) Regional blood flow by fractional distribution of indicators. *Am. J. Physiol.* **193**, 161–166.

12. Does increased colonic motility affect colonic absorption?

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The relationship between colonic motility and absorption is obscure. It is generally assumed that increased motility resulting in segmentation slows transit and hence allows extra time for absorption to take place (Wangel and Deller, 1965). Nevertheless, motor disorders of the colon are frequently associated with alternating constipation and diarrhoea. In this study the effect of increased colonic motility *per se* on absorption was determined.

Slow wave electrical activity was measured along the intact colon in 3 dogs and from Thiry–Vella loops in 3 dogs by serosal silver/silver chloride electrodes. Intraluminal pressure was simultaneously measured using thin, open-ended tubes. In each study two 20-min basal recordings were obtained and absorption of Na^{+}, Cl^{-}, H$_2$O, K^{+}, HCO$_3^-$ and HN$_3$ calculated. The colon was then stimulated for two 20-min periods using 6/min pulse waves (10 mA, 100 ms), during which time the absorption studies were repeated. Stimulation frequently produced forward pacing of the colon and significantly increased motility on each occasion (basal percentage motility 8·76 per cent ±2·06 s.e. mean, stimulation 41·31 per cent ±5·49 s.e. mean, $P<0·001$).

Increased colonic motility statistically significantly increased colonic absorption of Na^+, Cl^- and H_2O, irrespective of alteration in transit time. These data suggest that motor upsets in the colon may result in reduced stool weight without a change in transit time.

	Mean basal	Mean stimulation
Na^+ (μmol)	3·57	8·24*
Cl^- (μmol)	20·71	25·46*
H_2O (ml)	0·07	0·10*
K^+ (μmol)	−0·73	−0·99
HCO_3^- (μmol)	−6·42	−5·93
NH_3 (μmol)	7·51	8·16

* $P<0·01$.

All results = absorption cm^{-2} h^{-1}.

WANGEL A. G. and DELLER D. J. (1965) Intestinal motility in man—mechanism of constipation and diarrhoea with particular reference to the irritable colon syndrome. *Gastroenterology* **48**, 69–84.

13. Carcinoma of the large bowel and faecal bile acids

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Faecal bile acid concentrations of patients with large bowel carcinoma were elevated in studies using enzymatic assay (Hill et al., 1975) or gas–liquid chromatography (Reddy and Wynder, 1977). Were these raised concentrations the result of the tumour rather than its cause?

Patients with large bowel carcinoma ($n=19$) were studied before operation and 10 were also studied 8–26 weeks postoperatively. They were compared with healthy controls ($n=19$) and with 20 patients who had undergone local excision of large bowel adenoma. Faecal 3-hydroxy bile acids were estimated enzymatically (Hill and Aries, 1971), omitting the reduction of the faecal extract with borohydride.

In cancer patients the preoperative bile acid concentration (26·3±2·5 μmol/g dry faeces; mean±s.e. mean) was not significantly different from that of controls (28·1±2·7) or adenoma patients (25·4±2·3). When the 10 cancer patients were compared preoperatively (26·8±3·3) and postoperatively (25·2±4·3), the difference in means was not significant. In 5 patients the bile acid concentration fell after surgery and in 5 it rose.

This study does not show the expected elevation of 3-hydroxy bile acids in patients with cancer of the large bowel nor does it suggest any consistent effect of surgery on faecal bile acid concentration.

HILL M. J. and ARIES V. C. (1971) Faecal steroid composition and its relationship to cancer of the large bowel. *J. Pathol.* **104**, 129–139.

HILL M. J., DRASAR B. S., WILLIAMS R. E. O. et al. (1975) Faecal bile acids and clostridia in patients with cancer of the large bowel. *Lancet* **1**, 535–539.

REDDY B. S. and WYNDER E. L. (1977) Metabolic epidemiology of colon cancer. Faecal bile acids and neutral sterols in colon cancer patients and patients with adenomatous polyps. *Cancer* **39**, 2533–2539.

14. Replacement of colonic mucosa by free and pedicled grafts of ileal mucosa in the dog

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Radical surgery for ulcerative colitis usually means panproctocolectomy and ileostomy. Since ulcerative colitis is primarily a mucosal disease, several workers have recently concentrated on procedures which remove the diseased rectal mucosa and restore gastrointestinal continuity by replacing it with full-thickness ileum (Martin et al., 1977; Johnston and Williams, 1978). In an attempt to improve these techniques, we have explored the feasibility of replacing the colonic mucosa with grafts of ileal mucosa alone.

Both free and pedicled autografts of ileal mucosa were grafted into Thiry–Vella loops of colon which had been denuded of mucosa and submucosa.

All the free grafts failed to survive (7 dogs) and histological examination confirmed graft rejection. All the pedicled grafts (7 dogs) were successful and retained the histological characteristics of normal ileum.

Net transport and bidirectional movement of sodium, potassium and water were measured using a perfusion technique (Krejs et al., 1977) in 6 dogs with pedicled grafts and 4 control dogs with intact ileal loops.

Net movement	Controls ($n=4$)	Pedicled grafts ($n=6$)	P
Na^+ (μmol cm^{-1} h^{-1})	−57·1±10·8	48·2±13·5	<0·001
K^+ (μmol cm^{-1} h^{-1})	−0·5±0·5	+2·5±0·7	<0·05
H_2O (μl cm^{-1} h^{-1})	−436±69	+139±40	<0·001

Mean±s.e. mean.

A negative value denotes absorption and a positive value, secretion.

We conclude that the mucosa of the colon can be replaced successfully by grafts of ileal mucosa provided that an intact blood supply is preserved. The graft, however, ceases to function normally, and secretes Na^+, K^+ and water. These observations may be relevant to the conservative surgical treatment of ulcerative colitis.

JOHNSTON D. and WILLIAMS N. S. (1978) Sphincter on the ileum: mucosal proctectomy and ileo-anal anastomosis for ulcerative colitis. *Gut* **19**, 990.

KREJS G. J., SEELIG L. L. and FORDTRAN J. S. (1977) Effect of protonated 2-4-6 triaminopyrimidine, a 'tight junction blocker', on intestinal transport in dog ileum. *Gastroenterology* **72**, 685–691.

MARTIN L. W., LECOULTRE C. and SCHUBERT W. K. (1977) Total colectomy and mucosal proctectomy with preservation of continence in ulcerative colitis. *Ann. Surg.* **186**, 477–479.

15. Pathogenesis of water retention with intravenous nutrition: a prospective clinical study

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Much of the weight gained by patients receiving intravenous nutrition is due to water retention. It is not known if this water accumulates inside or outside cells, and whether the retention is decreased by increasing the intravenous energy intake. In a prospective randomized study we measured changes in body composition (Hill et al., 1978) over a 14-day period in 16 patients who received 38·5±3·8 kcal kg^{-1} d^{-1} (group I) and compared these with the changes that occurred in 16 closely matched patients who received 53·5±5·0 kcal kg^{-1} d^{-1} (group II).

Group I patients lost body protein (−0·62±0·91 kg, $P<0·05$) although body weight (0·13±3·5 kg, n.s.), body fat (0·13±0·88 kg, n.s.) and body water (0·85±3·03 kg, n.s.) did not fall. Group II patients gained body weight (3·6±2·3, $P<0·001$), body protein (0·44±0·75 kg, $P<0·05$), body fat (0·80±0·96 kg, $P<0·01$) and body water (2·3±2·4 kg, $P<0·01$).

Half the patients in each group consented to muscle biopsy, which was analysed for water and electrolytes. The muscle water content is expressed as kg of intracellular water (ICW) and kg of extracellular water (ECW) per kilogramme of fat-free dry weight. The patient's own intracellular potassium concentration and total body potassium were used to derive whole body ICW and ECW.

Group I patients, who lost protein, demonstrated a reduction of ICW and an expansion of ECW. Group II patients, who

	Whole body		Muscle	
	ICW*	ECW*	ICW*	ECW*
Group I ($n = 8$)				
$\bar{x}$	−2·2	+3·4	−0·48	+0·54
s.d.	±1·5	±3·2	±0·41	±0·69
P	<0·01	<0·05	<0·01	n.s.
Group II ($n = 7$)				
$\bar{x}$	+1·5	+2·1	−0·12	−0·04
s.d.	±2·7	±4·3	±0·56	±0·91
P	n.s.	n.s.	n.s.	n.s.

* Expressed as kg/kg fat-free dry weight.

gained protein, had appropriate increases of both ICW and ECW. The results suggest that water retention in patients receiving intravenous nutrition occurs in the extracellular compartment and this can be decreased by increasing the intravenous energy intake.

HILL G. L., MCCARTHY I. D., COLLINS J. P. et al. (1978) A new method for the rapid measurement of body composition in critically ill surgical patients. *Br. J. Surg.* **65**, 732–735.

16. A pocket calculator program for intravenous requirements

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The provision of patients' daily requirements of fluid, electrolytes and nutrition is often made on a rule-of-thumb basis or using 'standard' regimens. Although acceptable for fit patients in the short term, this basis is unsatisfactory for those with prolonged fluid balance problems who require individual prescription.

Such calculation, although not difficult, is time-consuming; the recent marketing of card-programmable pocket calculators, however, has made the rapid estimation of individually tailored requirements possible.

A program was written to calculate water, electrolyte, calorie and nitrogen requirements from patients' measured fluid input and output and serum electrolyte concentrations. Inbuilt correction factors were included to account for unknown or unmeasured losses.

The composition of 'standard' 24-h regimens prescribed at the bedside was compared with the calculator estimation for 6 patients requiring parenteral nutrition. The percentage differences for each patient were calculated. In general, the 'standard' regimens tended to overestimate requirements of water and underestimate calcium, magnesium, calories and nitrogen, confirming the tendency of patients receiving parenteral nutrition to become overhydrated (Collins et al., 1978).

It is suggested that the advantage of individually tailored fluid therapy regimens can be extended to all patients by the use of a suitably programmed pocket calculator.

COLLINS J. P., OXBY C. B. and HILL G. L. (1978) Intravenous amino acids and intravenous hyperalimentation as protein-sparing therapy after major surgery. *Lancet* **1**, 788–791.

17. The value of early postoperative feeding with an elemental diet through a fine-needle catheter jejunostomy following major colorectal surgery

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It has been suggested that the infusion of an elemental diet in the period after major surgery minimizes nitrogen loss and is of clinical benefit (Sagar et al., 1978).

We conducted a prospective clinical trial to assess the nutritional benefits and clinical values of giving the elemental diet by continuous infusion through a fine-needle catheter jejunostomy during the first 14 days after major colorectal surgery. Twenty patients thus treated were matched with 20 control patients for sex, age, weight, degree of weight loss, diagnosis and operation. Body weight, arm muscle circumference (AMC) and total body potassium (TBK) were measured before and 2 weeks after surgery.

To date the results show that the technique of feeding postoperative patients through a fine-needle catheter jejunostomy is simple and practical. Our 20 patients received an average of 1650±284 kcal/d of the elemental diet over a mean time of 10·2±3·2 days. The elemental diet patients maintain their body weight and body cell mass (TBK) better than the control patients. However, the administration of the elemental diet is not associated with any demonstrable clinical benefit in terms of duration of postoperative hospital stay, abdominal wound healing and complication rate.

	Control ($n = 20$)	Elemental ($n = 20$)
Δ Body weight (kg)	− 26±0·4*	−0·6±0·4**
Δ TBK (mmol)	−283±36*	−61±43**
Δ Arm muscle circumference (cm)	− 0 8±0·2*	−0·3±0 2**

Results expressed as a mean±s.e. mean.
* Significant at 1% level.
** Not significant (paired *t* test).

SAGAR S., HARLAND P. and SHIELDS R. (1978) Value of early postoperative feeding with an elemental diet. *Br. J. Surg.* **65**, 815–816.

18. Effect of different calorific doses of carbohydrate infusion on nitrogen excretion after surgery

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The protein-sparing effect of low dose carbohydrate infusion in starving man (circa 6 kcal/kg bodyweight) was observed by Gamble in 1946 but the effect of variable high calorific regimens of carbohydrates without concomitant fat or nitrogen in postoperative patients is less well documented (Giddings, 1974; Long, 1977).

We have studied nitrogen excretion after surgery at three calorific levels—6, 25, 40 kcal of glucose kg^{-1} d^{-1} for the first 2 days postoperatively. There were 6 patients in each group having surgery of comparable severity (e.g. cholecystectomy, PGV). Urinary nitrogen was estimated by the Kjeldahl method. The results are shown in the Table.

	6 kcal	25 kcal	40 kcal
Day 1	0·24 ±0·07	0·15 ±0·09	0·15 ±0·04
Day 2	0·27 ±0·07	0·19 ±0·04	0·14 ±0·02

Nitrogen excretion in g/kg fat-free mass (mean ±s.d.).

Serum insulin levels were highest in the 40 kcal/kg group. Carbohydrate infusion has a progressive nitrogen-sparing effect quantitatively comparable to that achieved by intravenous amino acid infusion (Blackburn, 1977). If nitrogen-sparing is desired postoperatively, it can be achieved by the use of carbohydrate alone.

BLACKBURN G. (1977) In: RICHARDS J. R. and KINNEY J. M. (ed.) *Nutritional Aspects of Care of the Critically Ill.* Edinburgh, Churchill Livingstone, pp. 305–330.
GIDDINGS A. E. B. (1974) Control of plasma glucose in the surgical patient. *Br. J. Surg.* **61**, 787–792.
LONG J. M. (1977) In: RICHARDS J. R. and KINNEY J. M. (ed.) *Nutritional Aspects of Care of the Critically Ill.* Edinburgh, Churchill Livingstone, pp. 331–334.

19. Is cholestasis in severely ill patients due to infection or malnutrition?

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Intrahepatic cholestasis and abnormal liver function are common in severely ill patients. The cause is unknown, but factors, which often occur in combination, include parenteral nutrition, hypoxia, malnutrition and infection (Sitges-Creus et al., 1978). This study compared liver function in non-septic, malnourished patients, severely septic patients and patients recovered from sepsis with that in healthy control subjects of similar age and sex. No patients had received parenteral nutrition.

Table I: COMPARISON OF THE GROUPS

	C ($n = 10$)	M ($n = 7$)	S ($n = 10$)	S-r ($n = 4$)
Age (yr)	60±2	62±5	55·4±5·1	56·0±4·0
Weight (kg)	69±5	50±4**	59·3±3·3	56·0±4·0
Weight loss (%)	3±5	26±4**	18±4*	21±7*

C, control; M, malnourished; S, septic; S-r, septic, recovered. All mean±s.e. mean. * $P<0·05$; ** $P<0·02$; *** $P<0·001$ compared with control.

Table II: RESULTS

	C	M	S	S-r
Albumin (g/l)	40±1	37±1	29±2**	38±1
Cholesterol (mmol/l)	5·3±0·5	4·5±0·3	3·2±0·4***	5·0±0·8
Bilirubin (μmol/l)	11±1	10±3	52±40	9±2
Alkaline phosphatase (i.u./l)	61±8	136±54	220±95**	60±21
GOT (i.u./l)	46±11	48±13	70±12**	25±7
Urea (mmol/l)	4·6±0·5	5·0±1·0	4·8±0·8	4·3±1·1

C, control; M, malnourished; S, septic; S-r, septic, recovered. All mean±s.e. mean. * $P<0·05$; ** $P<0·02$; *** $P<0·001$ compared with control.

Septic patients, unlike malnourished subjects, had decreased plasma concentrations of albumin and cholesterol and increased concentrations of bilirubin, alkaline phosphatase and GOT compared with control subjects. Following clinical recovery from infection, liver function tests returned to normal though weight loss was still evident several weeks later. These results suggest that abnormal liver function and cholestasis result from infection rather than from malnutrition. Infection should be carefully sought in patients receiving parenteral nutrition who develop abnormal liver function.

SITGES-CREUS A., CANADAS E. and VILAR L. (1978) In: JOHNSTON I. D. A. (ed.) *Advances in Parenteral Nutrition.* Lancaster, MTP Press, pp. 461–470.

20. The maximum activity of three key enzymes in human skeletal muscle and the effects of a course of intravenous nutrition

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It is not known if fundamental alterations in the maximum activity (MA) of Kreb's cycle and glycolysis occur in critically ill patients and whether these pathways are influenced by intravenous nutrition. It has been shown in both vertebrates and invertebrates (Crabtree and Newsholme, 1972; Read et al., 1977) that the MA of α-ketoglutarate dehydrogenase (α-KGD-ase) and phosphofructokinase (PKF) represent the MA of these pathways *in vivo*.

We have studied the MA of these enzymes in chopped skeletal muscle and also the MA of fructose 1,6-diphosphatase (FDPase) as an indicator of substrate cycle activity in 9 critically ill patients before and after intravenous nutrition and in 12 control subjects. The results were as follows:

	α-KGDase*	PFK*	FDPase*
Surgical pre. IVN (1)	0·68±0·13	17·9±2·1	0·57±0·10
Surgical post. IVN (2)	0·75±0 06	20·7±1·2	0·45±0·04
Control (3)	0·86±0·09	23·9±1·9	1·31±0·16
P 1 *v.* 2	n.s.	n.s.	n.s.
P 1 *v.* 3	n.s.	n.s.	<0·02
P 2 *v.* 3	n.s.	n.s.	<0·01

Values for MAs are mean±s.e. mean.
* μmol min^{-1} g muscle^{-1}.

There were no significant differences in the mean MA of α-KFDase and PFK in the muscle of patients before or after intravenous nutrition and between the patients and controls. However, the mean MA of FDPase was significantly less in the patients.

It is conlcuded that the MA of both Kreb's cycle and the glycolysis is not impaired either before or after intravenous nutrition. However, since FDPase was significantly lower both before and after intravenous nutrition the possibility exists that the kinetics of glucose flow are altered within skeletal muscle in these patients.

CRABTREE B. and NEWSHOLME E. A. (1972) The activities of phosphorylase, hexokinase, phosphofructokinase, lactate dehydrogenase and the glycerol 3-phosphate dehydrogenase in muscles from vertebrates and invertebrates. *Biochem. J.* **126**, 49–58.

READ G., CRABTREE B. and SMITH G. H. (1977) The activities of 2-oxoglutarate dehydrogenase and pyruvate dehydrogenase in hearts and mammary glands from ruminants and non-ruminants. *Biochem. J.* **164**, 349–355.

21. Surgeons heart rates and surgical performance: a double-blind trial of oxprenolol

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Surgeons experience a tachycardia during operating which is abolished by β-blockade (Foster et al., 1978). We report a prospective double-blind trial in which senior registrars and consultants took 40 mg oxprenolol or a matching placebo before four operating lists. During one case in each list, three tests of surgical performance were made. Suturing accuracy was assessed using a method which required ten sutures to be placed 1 cm apart. Tremor was measured during the passage of a curved needle through a series of graded holes using an electronic contact counter. Concentration and reaction time over a 2-min period were assessed using the 'four choice' test (Wilkinson and Houghton, 1975). Heart rates were recorded throughout operating sessions using the medilog ambulatory system. After each list, surgeons completed visual analogue scores summarizing their subjective feelings and were asked which medication they had taken.

During the operations after oxprenolol, heart rates averaged 83 (±8·1 s.d.) per minute for all surgeons, and after placebo 120 (±10·5 s.d.) per minute (paired $t = 7·5$, $P<0·001$). In the tests of tremor and suturing accuracy, there was no difference between the oxprenolol and placebo groups, but reaction time was slower for each surgeon ($P<0·01$) for the oxprenolol group. The tests showed consistency for each surgeon. Subjective feelings were not affected by either preparation but surgeons were surprisingly unaware that they had taken oxprenolol.

FOSTER G. E., EVANS D. F. and HARDCASTLE J. D. (1978) Heart rates of surgeons during operating and other clinical activities and their modification by oxprenolol. *Lancet* **1**, 1323–1325.

WILKINSON R. T. and HOUGHTON D. (1975) Portable four choice reaction time test with magnetic tape memory. *Behaviour Res. Methods Instrument.* **7**, 441–446.

22. The use of cooled irrigating fluid for transurethral resection of the prostate

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Cockett et al. (1961) reported no difference in blood loss during transurethral resections of the prostate using cooled irrigation fluid (3 °C) compared with fluid at ambient temperature. Conversely, Serrao et al. (1976) reported that cooling of the irrigation fluid to 2 °C reduced both blood loss at operation ($P<0·001$) and irrigant volume ($P<0·002$).

Forty patients were randomly divided into two groups before transurethral resection of the prostate. In the first group ($n = 20$) the irrigation fluid was cooled to 8 °C, the lowest temperature at which the resectoscope could be comfortably held, and in the second ($n = 20$) the fluid was at ambient temperature.

Irrigation fluid was maintained at a constant temperature by passing it through a heat exchanger in a cooled water bath. We monitored the fluid temperature as it entered the resectoscope and the oesophageal temperature of the patient. We also measured the volume of irrigation fluid used, the blood loss both during and after resection and the weight of resected tissue.

The parameters measured covered a wide range of values and non-parametric analysis was used to analyse the results. Significantly lower volumes of cooled fluid were required during transurethral resection of the prostate (Mann-Whitney U test, $P<0{\cdot}002$), and the clarity of the operative field was improved.

These results suggest that advantages may be gained by the use of cooled irrigation fluid during routine transurethral resection of the prostate.

COCKETT A. T. K., SCHULTZ J. and FRANKS D. (1961) Use of refrigerated solutions during transurethral surgery. *J. Urol.* **85**, 632–635.

SERRAO A., MALLIK M. K., JONES P. A. et al. (1976) Hypothermic prostatic resection. *Br. J. Urol.* **48**, 685–687.

23. The behaviour of antibiotics in bone cements

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This paper describes an original study of the behaviour of the antibiotics diethanolamine fusidate (Fucidin), diethanolamine fusidate and erythromycin, clindamycin, cephazolin sodium (Kefzol) and gentamicin, when mixed with each of the bone cements CMW, Palacos, Simplex and Sulfix.

Each antibiotic bone cement combination was inserted into the reamed medullary canal of one femur of each of 5 live rabbits. A metal cannula with side-wall perforations was placed at each cement bone interface, with its proximal end lying subcutaneously. Using normal saline, percutaneous lavage through the cannulas was carried out at regular intervals postoperatively. The lavage fluid was assayed for antibiotic activity, using the appropriate test organisms. Duration of release, in days is shown.

Cement	DF	DF+E	C	CS	G
CMW	140±20	16±3	14±4	8±3	79±20
Palacos	73±15	30±20	6±3	13±3	56±20
Simplex	56±7	31±14	24±7	7±3	75±12
Sulfix	50±20	14±10	7±3	15±3	54±20

DF, Diethanolamine fusidate; DF+E, diethanolamine fusidate+erythromycin; C, clindamycin; CS, cephazolin sodium; G, gentamicin.
All results mean±s.e. mean.

These results suggest that CMW, Palacos and Simplex are satisfactory antibiotic carriers. Release levels of cephazolin sodium and clindamycin were short-lived but high. Clinical experience in the prophylaxis against infection in joint replacement has not yet shown whether this is desirable.

Immunological tolerance of the various antibiotic cement combinations was investigated by intradermal injections of dilutions of the antibiotics. Assessment by skinfold measurements and by clinical appearance showed no evidence of allergy development. Liver and kidney biopsies showed no signs of cumulative antibiotic toxicity.

24. Peritoneal fibrinolysis and adhesion formation

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The pathogenesis of intraperitoneal adhesions is poorly understood. As part of the initial response to injury, fibrin is deposited on serosal surfaces resulting in a fibrinous adhesion. Prevention of the development of fibrous adhesions depends on the removal of this fibrin before it is invaded by fibroblasts.

A quantitative technique (Raftery, 1977) has been used to measure the fibrinolytic activity in healing unsutured peritoneal defects in rats. These defects heal with little or no adhesion formation. Fibrinolytic activity is lowest at 24 h and thereafter increases, until at 8 days, when peritoneal healing is complete (Raftery, 1973), it is still greater than that of normal peritoneum. Peritoneal fibrinolytic activity has also been measured following four other types of peritoneal insult; diathermy wounds, free peritoneal grafts, ischaemic bowel and bile peritonitis. The degree of reduction of peritoneal fibrinolytic activity has been compared with that of the unsutured peritoneal defect, and has been correlated with the incidence of adhesions. The results are shown in the Table. Normal peritoneum has a fibrinolytic activity of 0·075±0·006 Ploug units.

Insult	Lowest recorded FA*	Incidence of adhesions
Unsutured defect	0·036±0·005	5%
Free graft	0·013±0·009 ($P<0{\cdot}01$)	100%
Diathermy	0 ($P<0{\cdot}001$)	95%
Ischaemic bowel	0·009±0·005 ($P<0{\cdot}001$)	100%
Bile peritonitis	0·033±0·014 ($P>0{\cdot}5$)	0%

* FA, Fibrinolytic activity in Ploug units, mean±s.d.

Adhesions occur in areas where peritoneal fibrinolytic activity is significantly reduced. The results suggest that fibrinolytic agents may be beneficial in the prophylaxis of adhesions.

RAFTERY A. T. (1973) Regeneration of parietal and visceral peritoneum. *Br. J. Surg.* **60**, 293–299.

RAFTERY A. T. (1977) A method for measuring fibrinolytic activity in a single layer of cells. *Br. J. Surg.* **64**, 825–826.

25. The effect of prophylactic cotrimoxazole on postoperative pulmonary complications

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Pulmonary complications following biliary surgery are common. Chest infection is usually associated with the presence of *Haemophilus influenzae* or *Streptococcus pneumoniae* in the sputum; both organisms are sensitive to cotrimoxazole. A controlled study was undertaken to assess the value of prophylactic cotrimoxazole in reducing these sequelae.

Sixty-eight consecutive patients undergoing elective cholecystectomy were randomized to receive either a single preoperative dose of cotrimoxazole or a placebo. Postoperative pulmonary complications were assessed using clinical criteria. Arterial blood-gas analysis was undertaken preoperatively and on days 1–4 postoperatively.

Thirty-six patients had no clinically significant postoperative pulmonary complications; 18 developed atelectasis and 14 chest infection. The pattern of arterial oxygen tensions in patients with pulmonary complications was significantly different from that in the uncomplicated group (Table). *H. influenzae* and *S. pneumoniae* were present in 8 of the 14 patients with chest infection.

	Arterial oxygen tensions†			
	Postop. day			
Group	1	2	3	4
No postoperative complications	83±2	85±2	87±2	93±2
Atelectasis	75±3*	78±3*	82±2	87±3
Chest infection	73±3**	70±3***	71±2***	75±3***

† Expressed as a percentage of preoperative value.
* $P<0{\cdot}05$; ** $P<0{\cdot}005$; *** $P<0{\cdot}001$.

Eleven of the 34 control patients developed chest infection, whereas only 3 of 34 patients receiving cotrimoxazole developed chest infection ($P<0{\cdot}05$).

These data suggest that a single prophylactic dose of cotrimoxazole significantly reduces respiratory morbidity following biliary surgery.

26. What patients recall of an intensive care unit

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One hundred consecutive patients were interviewed between the third and seventh days following their discharge from an intensive care unit. Their mean stay was 40 h (range 7–120).

The patients' recall of events was generally poor. Forty per cent were able to give a fair estimate (<50 per cent error) of the duration of their stay, while 20 per cent were unable to estimate at all or had no recollection of the unit.

Only 7 of 22 patients treated by assisted ventilation were able to recall the experience.

Ninety-three patients were able to comment on their recollection of nursing and medical staff. Of these 21 said they were given insufficient explanation, 17 that medical staff were 'not around when needed' and 7 that worrying details were discussed around their bed.

Of the factors provoking anxiety and worry, 32 patients complained of pain, 18 of lack of sleep and 18 of physiotherapy.

Factors that prevented or disturbed sleep were: inability to be comfortable, 55 patients; pain, 41; anxiety, 18; and the wearing of a mask, 17 patients.

Less than half of the patients said they were pleased to return to a general ward.

27. A randomized trial to compare oral with parenteral antibiotic prophylaxis in elective colonic resection

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A prospective randomized trial has compared oral ($n = 39$) with parenteral prophylaxis ($n = 42$) in elective colonic resection for malignant disease. Patients received metronidazole and kanamycin. Oral therapy was designed to reduce the bacterial flora of the colon (Goldring et al., 1975) without achieving therapeutic serum concentrations and systemic prophylaxis to provide adequate serum levels without altering the colonic microflora. Serum and colonic contents were sampled at operation for antibiotic assay and for counts of pathogenic bacteria in the colon. All patients with postoperative diarrhoea were investigated for faecal toxins and *Clostridium difficile* (George et al., 1978).

Oral preparation significantly reduced the counts of *Escherichia coli* (10^7 to 10^4) and *Bacteroides fragilis* (10^8 to 10^1) in the colon and did not achieve therapeutic serum levels. Nevertheless, high counts of resistant bacteria were observed in 14 (36 per cent) of the orally prepared patients. Intravenous prophylaxis achieved therapeutic serum levels but had no influence on colonic microflora. The overall rate of sepsis was 33 per cent in patients prepared orally compared with 11 per cent in patients receiving parenteral prophylaxis ($P < 0{\cdot}02$). Pseudomembranous colitis occurred in 6 patients receiving oral preparations but in none receiving systemic antimicrobials.

These results indicate that parenteral antibiotic prophylaxis is more effective at reducing sepsis and is less likely to be complicated by antibiotic resistance and pseudomembranous colitis than oral antimicrobial bowel preparation.

GEORGE R. H., SYMONDS J. M., DIMOCK F. et al. (1978) Identification of *Clostridium difficile* as cause of pseudomembranous colitis. *Br. Med. J.* **1**, 695.

GOLDRING J., SCOTT A., MCNAUGHT A. et al. (1975) Prophylactic oral antimicrobial agents in elective colonic surgery. *Lancet* **2**, 997–999.

28. The measurement of gastric emptying: a comparison of fixed scintillation detection and the double sampling technique

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The emptying of fluid meals can be accurately measured using a nasogastric tube (George, 1968; Hunt and Knox, 1968). Fixed scintillation detection has been shown to give similar information to external scanning using a gamma camera (Ostick et al., 1976), but has not been compared with intubation techniques.

The double sampling technique was compared with fixed scintillation detection in 14 normal subjects and in 15 patients who had had a vagotomy and drainage procedure. The 500-ml fluid meal contained emulsified milk, lactose and water. Double sampling using ^{51}Cr and scintillation detection using ^{113}In were performed simultaneously.

The times required to achieve 50 per cent emptying were compared. In normal subjects, both methods correlated well (Wilcoxon matched pairs test: $P < 0{\cdot}05$; Spearman's rank correlation coefficient: $r_s = 0{\cdot}856$). In operated subjects, rapid emptying of the initial part of the meal occurred. This caused problems in measurement, as scintillation detection readings are based on the initial reading following ingestion of the meal. This problem was overcome by relating all readings to an *in vitro* measurement of the meal to a 'water phantom' leading to good correlation at 50 per cent emptying (Wilcoxon: $P > 0{\cdot}05$; $r_s = 0{\cdot}625$).

The study of emptying of fluid meals gives more information about post-vagotomy syndromes than the study of mixed meals. External detection methods require modification when used in this situation.

GEORGE J. D. (1968) New clinical method for measuring the rate of gastric emptying: the double test meal. *Gut* **9**, 237–242.

HUNT J. J. and KNOX M. T. (1968) In: CODE C. F. (ed.) *Handbook of Physiology*, Section 6, Vol. IV. Washington, American Physiological Society, p. 1922.

OSTICK D. G., GREEN G., HOWE K. et al. (1976) Simple clinical method of measuring gastric emptying of solid meals. *Gut* **17**, 189–191.

29. Bile acids and colonic myoelectrical activity

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The cathartic property of bile acids can be explained by their inhibitory action on colonic absorption (Mekhjian and Phillips, 1971), but whether they alter motility and thereby influence colonic motor disorders by a similar pathway is not known.

In this study the effect of different concentrations of cholic, deoxycholic and chenodeoxycholic acid on colonic myoelectrical activity was recorded in four dogs. Slow wave electrical activity was measured using chronically implanted silver/silver chloride electrodes and intraluminal pressure simultaneously recorded with thin, open-ended tubes.

Measurements were obtained during a control period and following separate instillations of 5-mmol, 10-mmol and 15-mmol aliquots of each bile acid.

There was no statistically significant difference in percentage motility, motility index or basal pressure with either cholic or chenodeoxycholic acid. Deoxycholic acid (15 mmol), however, resulted in a marked increase in percentage motility on each occasion (control: median 4·1 per cent, range 0–23 per cent; after instillation: median 27 per cent range 20·6–45 per cent; $P < 0{\cdot}001$). This was accompanied by an increase in spike activity but no alteration in mean slow wave frequency. Cholestyramine inhibited the motor response. All concentrations of each bile acid inhibited Na, K and H_2O absorption.

Hence, only deoxycholic acid affects both colonic motility and absorption, presumably by different pathways, and may thus assume importance in the aetiology of colonic motor disorders.

MEKHJIAN N. and PHILLIPS S. (1971) Colonic secretion of water and electrolytes induced by bile acids. *J. Clin. Invest.* **50**, 1569–1572.

30. Extent of spread of a steroid-containing foam after intrarectal administration

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A steroid-containing foam (Colifoam) is currently being marketed for the local treatment of ulcerative colitis. It contains hydrocortisone acetate 10 per cent. Whilst steroid enemas are believed to spread to the splenic flexure (Flavell Matts, 1960) there is as yet no information on how far the foam spreads.

A standard dose of Colifoam was labelled with technetium ($^{99}Tc^{m}$ 100 μCi), which was adsorbed on to microspheres of Amberlite resin (200 mesh) distributed through the foam. Preliminary studies show the spread of radioactivity within the foam to be even. The labelled dose was given to 12 subjects, 4 with known ulcerative colitis and 8 subjects with normal bowel habit. The subjects were scanned with a gamma camera after 15 min, 2 h and 4 h; between scans the subjects were mobile.

Considerable variation was observed in the immediate spread of foam after its administration (9·1 cm±s.d. 3·7). No significant further spread of the foam was observed at 2 h and 4 h following administration. There was no difference in the behaviour of the foam control subjects and those with colitis.

These results show that whilst there is considerable variation in the immediate spread of the foam following administration there is no significant further spread with time and it is doubtful if the foam ever leaves the rectum.

FLAVELL MATTS S. G. (1960) Local treatment of ulcerative colitis with prednisolone-21-phosphate enemata. *Lancet* 1, 517–519.

31. The effect of highly selective vagotomy and truncal vagotomy on the lower oesophageal sphincter

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Significant gastro-oesophageal reflux often occurs after truncal vagotomy and drainage and this may be due to shortening of the lower oesophageal pressure zone (LOPZ) postoperatively (Thomas and Earlam, 1973). A 25 per cent incidence of gastro-oesophageal reflux has been reported following highly selective vagotomy (Temple and McFarland, 1975), but evidence of incompetence of the LOPZ after this operation is lacking.

The length and resting pressure produced by the LOPZ was measured by manometry using the station pullthrough technique in two groups of subjects:

1. Nineteen healthy volunteers who had no evidence of upper gastrointestinal disease (normal group).
2. Twenty patients studied immediately before and 3 months after surgery for duodenal ulceration, 14 having had a PGV and 6 having had a TV+P.

Before operation, the length and pressure of the LOPZ in patients with a duodenal ulcer were similar to the normal group (Table). Postoperatively, no significant change was produced in either the length or pressure of the LOPZ by either PGV or TV+P.

We conclude that gastro-oesophageal reflux following PGV or TV+P is not related to surgically induced incompetence of the lower oesophageal sphincter as measured by either the length or resting pressure of the LOPZ.

		Duodenal ulcer ($n = 20$)		
			Postop.	
LOPZ	Normal ($n = 19$)	Preop.	PGV ($n = 14$)	TV+P ($n = 6$)
Pressure (mmHg±s.d.)	10·4±5·5	8·8±3·6	9·0±3·5	11·1±3·9
Length (cm)	3·4±0·5	2·9±1·1	3·1±0 8	3 2±0·5

TEMPLE J. G. and MCFARLAND J. B. (1975) Gastro-oesophageal reflux complicating highly selective vagotomy. *Br. Med. J.* 2, 168–169.

THOMAS P. A. and EARLAM R. J. (1973) The gastro-oesophageal junction before and after operations for duodenal ulcer. *Br. J. Surg.* 60, 717–719.

32. Basal gastrin-like bioactivity in normal subjects and duodenal ulcer patients

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Most reports agree that basal immunoreactive gastrin levels in normal subjects and duodenal ulcer patients are identical (McGuigan and Trudeau, 1973); these reports do not take the biological activity of the various immunoreactive gastrin molecules into account.

The use of non-quantitative bioassays and radioimmunoassays to compare normal subjects and duodenal ulcer patients has produced discrepancies suggesting the presence of a circulating gastric secretagogue in ulcer patients which appears not to be measured by radioimmunoassay (Hansky et al., 1974; Bugat et al., 1976).

A highly sensitive, quantitative, cytochemical section bioassay (Hoile and Loveridge, 1977) has been used to assess the gastrin-like activity in plasma from a group of normal subjects and a group of duodenal ulcer patients.

Blood was obtained from 24 fasting volunteers and from 15 fasting patients with proved duodenal ulceration. Heparinized plasma containing aprotinin (Trasylol) 1000 KIU/ml blood was used; this was stored at −70 °C until measurement. Synthetic human G-17-I or natural human G-17-I was used as a standard (these being equipotent in the cytochemical assay system). Each plasma was assayed at two dilutions (1 : 100 and 1 : 1000) and the mean taken for evaluation.

There was a highly significant difference between the basal plasma gastrin-like bioactivity in these two groups ($P<0·0012$).

	Gastrin-like bioactivity (pmol/l)	
Subjects	Mean (±s.d.)	Range
Normal ($n = 24$)	5·8±1·7	1·9–17·6
Duodenal ulcer ($n = 15$)	12·8±2·3	2·1–77·5

The plasma of fasting duodenal ulcer patients does contain a substance with a gastrin-like biological activity which is significantly in excess of that present in the plasma of normal volunteers.

BUGAT R., WALSH J. H., IPPOLITI A. et al. (1976) Detection of a circulating gastric secretagogue in plasma extracts from normogastrinaemic patients with acid hypersecretion. *Gastroenterology* 71, 1114–1116.

HANSKY J., ROYLE J. P. and KORMAN M. G. (1974) Comparison of bioreactive and immunoreactive gastrin. *Aust. J. Exp. Biol. Med. Sci.* 52, 841–846.

HOILE R. W. and LOVERIDGE N. (1977) Early results from the cytochemical section bioassay for gastrin. *Br. J. Surg.* 64, 293.

MCGUIGAN J. E. and TRUDEAU W. L. (1973) Differences in rates of gastrin release in normal persons and patients with duodenal ulcer disease. *N. Engl. J. Med.* 288, 64–66.

33. Normovolaemic haemodilution in the treatment of intermittent claudication

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We attempted to improve the leg blood flow in patients unsuitable for reconstructive surgery by normovolaemic haemodilution down to a packed cell volume of 35 per cent. This technique has recently been shown to improve oxygen delivery to the brain in patients with cerebral ischaemia (Thomas et al., 1977).

Apart from full haematological and haemorheological investigations, patients' blood flow was assessed objectively by ankle pressure measurements and plethysmography before and after stress. After base line measurements, 500 ml of blood were withdrawn weekly and replaced with dextran 70 in normal saline until the packed cell volume was 35 per cent. Eight of the 11 patients reported a subjective improvement and there was no change in the other 3. On average, the peak calf blood flow during reactive hyperaemia doubled after haemodilution. As the haemoglobin concentration was only lowered by 20 per cent, there was presumably an increase in oxygen delivery.

THOMAS D. J., MARSHALL J., ROSS RUSSELL R. W. et al. (1977) Effect of haematocrit on cerebral blood flow. *Lancet* 2, 941–943.

34. A new classification for duodenitis

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The histopathological definition and the clinical significance of duodenitis are controversial. In an attempt to clarify these problems duodenal biopsies obtained at 75 oesophagogastroduodenoscopies (OGD) on 54 patients were examined after staining with haematoxylin and eosin (HE) for mucus glycoproteins (mucins) and for reticulin.

To assess the apparent degree of abnormality a scoring system has been devised: from 0 to 11 for the HE section; 0–5 for mucins; 0–2 for reticulin. Patients with abdominal pain but normal double contrast barium meals and normal appearance at OGD were used as a 'control' group. The average score for 45 biopsies was 2.

Five patients with active duodenal ulcers at the time of OGD had an average score of 11. The most striking features were an increase in the proportion of neutral mucins as the HE picture became more inflamed. The average score for the 5 duodenal biopsies from patients with gastric ulcers was 1. The score in those with active duodenal ulcers was different both from the control and gastric ulcer groups ($P<0\cdot001$, $P=0\cdot01$ respectively). No difference could be shown between the scores in the control group and the gastric ulcer group.

There were 7 biopsies from patients with frank duodenitis endoscopically but no ulcer craters nor abnormal double contrast barium meals; the average score was 10. This was different from the control and gastric ulcer group ($P<0\cdot001$, $P<0\cdot01$ respectively) but not from the duodenal ulcer group.

It is suggested that it is no longer adequate when studying the dyspeptic patient to restrict consideration of the duodenal mucosa to the presence or absence of a chronic ulcer crater.

35. Pelvi-ureteric junction obstruction: obstructive uropathy versus obstructive nephropathy, a new technique of assessment

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One of the commonest and most difficult decisions in urology is when to operate on a kidney apparently obstructed at the pelvi-ureteric junction. We have assessed 23 patients pre- and postoperatively by three methods:

1. Diuretic radiography.
2. Direct measurement of intrarenal pelvic pressure by needle puncture (Whitaker, 1973).
3. Gamma camera renography using computerized deconvolution analysis to quantitate separately isotope transit times across the parenchyma and across the collecting system.

It was found that:

1. Diuretic urography and direct pressure measurement correlate well (Whitfield et al., 1977).
2. Of the 23 patients who were radiologically and urodynamically obstructed and who underwent surgery, 13 were renographically obstructed preoperatively in that parenchymal isotope transit time was prolonged—an obstructive nephropathy. All 9 returned to normal postoperatively. The remaining 4 patients showed normal parenchymal isotope transit time but prolonged isotope transit time through the collecting system—an obstructive uropathy.

Of the 10 cases not operated upon who were radiologically and urodynamically normal or equivocal, 3 had an obstructive nephropathy renographically. In all 3 significant deterioration in percentage renal function on the affected side has been found at follow-up.

The important practical and functional distinction between obstructive uropathy and obstructive nephropathy can be made by a non-invasive technique.

WHITAKER R. H. (1973) Methods of assessing obstruction in dilated ureters. *Br. J. Urol.* **45**, 15–22.

WHITFIELD H. N., BRITTON K. E., KELSEY FRY I. et al. (1977) The obstructed kidney: correlation between renal function and urodynamic assessment. *Br. J. Urol.* **49**, 615–619.

36. The duodenal brake mechanism in man

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Isotonic saline empties from the stomach at the same rate after proximal gastric vagotomy and pyloroplasty as after proximal gastric vagotomy (PGV), but hypertonic dextrose empties more rapidly after PGV and pyloroplasty (Faxén et al., 1973). Therefore, the pylorus appears important in the control of emptying of hypertonic dextrose.

To determine how the pylorus controls the emptying of hypertonic dextrose, we have used a technique that continuously records the intraluminal pressures in the antrum, pylorus and duodenal bulb. We have compared the effects on gastroduodenal motility of intragastric infusion of isotonic saline (22 studies in 15 normal subjects) and of intragastric infusion of 10 per cent dextrose (10 studies in 10 normal subjects).

Compared with saline, dextrose reduced the incidence of antral contractions ($P<0\cdot02$) and increased the incidence of pyloric contractions (but not significantly, $P<0\cdot1$). Dextrose produced rhythmic, independent contractions of the pylorus in 7 of the 10 studies compared with none of the 22 during saline infusions ($P<0\cdot0001$) and produced an elevated pyloric basal pressure (5–10 cmH_2O) in 3 out of 10 compared with none out of 22 during saline infusion ($P=0\cdot02$).

During saline infusion the pylorus contracted as part of a unit comprising the whole gastroduodenal region, but during dextrose infusion it contracted independently. This independent action is probably the mechanism that controls the emptying of hypertonic dextrose and is disrupted by pyloroplasty.

FAXÉN A., DOLLEVAL G., KOCK N. G. et al. (1973) The influence of pyloroplasty on gastric emptying after parietal cell vagotomy. *Scand. J. Gastroenterol.* **8**, Suppl. 20, pp. 14–15.

37. A variant of intestinal metaplasia associated with gastric carcinoma. A premalignant lesion?

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Intestinal metaplasia is frequently associated with gastric carcinoma, but is also common in specimens showing only benign lesions (Morson, 1955). Intestinal metaplasia typically resembles the small intestine, though variants indistinguishable from the colon have been described. Another incomplete form with features of both gastric and intestinal epithelia has been noted (Goldman and Ming, 1968).

Gastrectomy specimens, including 35 cases of peptic ulcer and 32 of carcinoma, were investigated histologically and histochemically to demonstrate any association between carcinoma and a specific variant of intestinal metaplasia. Twenty-one cancers were bordered by severe intestinal metaplasia. In 16 this resembled colonic mucosa histochemically, showing marked sulphomucin secretion. Sulphomucins were most prominent in columnar-shaped cells in between goblet cells. Thirteen cases of peptic ulcer showed severe intestinal metaplasia, the distal antrum being the usual site of involvement. The metaplastic epithelium resembled small intestine histochemically, sialomucins predominating. Only 2 cases showed more than a trace of sulphomucin.

We consider this variant of intestinal metaplasia to be a premalignant lesion, rather than a non-specific response to carcinoma, for we have noted adenomatous polyps arising from a similar epithelium. These findings may be of use in the interpretation of gastric biopsies, possibly permitting early detection of cancer.

GOLDMAN H. and MING S. C. (1968) Fine structure of intestinal metaplasia and adenocarcinoma of the human stomach. *Lab. Invest.* **19**, 203–210.

MORSON B. C. (1955) Intestinal metaplasia of the gastric mucosa. *Br. J. Cancer* **9**, 365–376.

38. Acid phosphatase after examination of the prostate

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There is a widely held belief that rectal examination of the prostate causes a rise in serum acid phosphatase. Recently this has been questioned (Shuttleworth and Blandy, 1976). We have measured serum tartrate-labile acid phosphatase (TLAP) in relation to routine rectal examination and transurethral resection of the prostate using an autoanalyser method for determining TLAP (Warren and Moss, 1977). Blood samples were first taken before and 5 min after examination, and on the first and fourth mornings afterwards.

Three groups were studied: men with benign enlargement of the prostate, 20 men with carcinoma of the prostate; 18 normal men. There was no difference in any group in TLAP before and after rectal examination. Transurethral resection of the prostate produced a rapid large rise, which had returned to normal the following morning. The assay was shown, by internal and external comparison, to be reliable and accurate.

The known instability of acid phosphatase at 37 °C in alkaline solution (Woodard, 1959) makes it probable that enzyme released into the circulation is rapidly destroyed. We have shown this to be so after transurethral resection of the prostate. Rectal examination does not raise TLAP and there is no need to delay blood sampling following this manoeuvre.

Group	Mean TLAP (i.u./l) Before	5 min after
Benign ($n = 31$)	1·0	1·0
Carcinoma ($n = 20$)	13·3	13·7
Normal ($n = 18$)	0·7	0·7

SHUTTLEWORTH K. E. D. and BLANDY J. P. (1976) Carcinoma of the prostate. In: BLANDY J. P. (ed.) *Urology*. Oxford, Blackwell, p. 938.

WARREN R. J. and MOSS D. W. (1977) An automated continuous monitoring procedure for the determination of acid phosphatase activity in serum. *Clin. Chim. Acta* **27**, 179–188.

WOODARD H. W. (1959) The clinical significance of serum acid phosphatase. *Am. J. Med.* **27**, 902–910.

39. Psychiatric morbidity associated with adjuvant chemotherapy following mastectomy for breast cancer

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Although systemic chemotherapy improves the prognosis after radical mastectomy, little information is available on the quality of survival (British Breast Group, 1976). An existing trial of adjuvant chemotherapy in stage II breast cancer provided an opportunity to examine the prevalence of psychiatric disorder in patients randomly allocated to receive chemotherapy (C), radiotherapy followed by chemotherapy (RT+C) or radiotherapy (RT) following simple mastectomy and axillary clearance.

Preliminary results from two psychiatric self-rating scales are presented: the General Health Questionnaire (GHQ) (Goldberg, 1972), which provides a non-specific measure of psychiatric morbidity, and the Leeds Self-assessment of Depression (LSD) and Anxiety (LSA) General Scales (Snaith et al., 1976). Two groups of survivors were compared at 1 year and at 18 months: group I (C and RT+C) and group II (RT). At 1 year the GHQ showed 39 per cent of group I with scores within the psychiatric illness range compared with 13 per cent of group II: at 18 months, 20 per cent of group I and none in group II. The LSD revealed 27 per cent of group I compared with 13 per cent of group II to have clinical depression at 1 year: at 18 months, 21 per cent in group I and none in group II. Groups I and II both had substantial proportions with pathological anxiety on the LSA—50 per cent and 38 per cent respectively at 1 year and 53 per cent and 25 per cent respectively at 18 months.

Comparing mean scores (Table), psychiatric morbidity, particularly depression, is significantly greater in patients completing a 1-year course of chemotherapy than in those who had radiotherapy alone; this difference is still evident at 18 months.

	GHQ	LSD	LSA
Group I ($n = 24$)			
12 mth	14·0±3·2	5·7±0·9	7·5±0·9
18 mth	9·1±3·2	3·8±0·9	8·0±1·1
Group II ($n = 15$)			
12 mth	4·3±1·6	2·5±0·7	6·6±1·1
18 mth	2·0±0·9	1·4±0·5	5·6±0·6
P I *v.* II			
12 mth	<0·01	<0·05	n.s.
18 mth	<0·05	<0·02	n.s.

Values are mean±s.e. mean.

BRITISH BREAST GROUP (1976) Systemic chemotherapy in early breast cancer. *Br. Med. J.* **2**, 861.

GOLDBERG D. P. (1972) *The Detection of Psychiatric Illness by Questionnaire*. London, Oxford University Press.

SNAITH R. P., BRIDGE G. W. K. and HAMILTON M. (1976) The Leeds scales for the self-assessment of anxiety and depression. *Br. J. Psychiatr.* **128**, 156–165.

40. The effect of hypoxia and hypoxic sensitizers on murine colonic tumour cultures (MAC 15)

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It is likely that there are cells within solid tumours which are severely hypoxic, and it is believed that these tumour cells are radio- and chemoresistant. Agents such as metronidazole and misonidazole appear to potentiate the action of ionizing radiation on hypoxic cells and there is some suggestion that these agents may have a cytopathic action of their own which could be helpful in tumour control.

Monolayer cultures were derived from colonic tumour implants (MAC 15) carried in NMRI mice. Cell survival in cultures was measured by tritiated thymidine and leucine incorporation. Cell cultures were exposed to severe hypoxia (4 parts O_2 per thousand) for 8, 16 and 24 h and showed a pronounced fall in thymidine incorporation to 10 per cent of control levels with 24 h hypoxia, though leucine incorporation still continued at 60 per cent of normal levels. Extended hypoxia for 40 h completely suppressed growth from 3 of 6 tumours but 3 tumours contained cells which were capable of leucine incorporation at 50 per cent of the levels obtained in aerobic cultures of the same tumour. Thymidine incorporation was, however, completely suppressed.

The cytotoxic action of both metronidazole and misonidazole was tested against aerobic cultures of MAC 15 in concentrations ranging from 125 to 1000 μg/ml and found to reduce leucine and thymidine incorporation by only 10–30 per cent of control cultures. Metronidazole was tested against two hypoxic tumours in culture and found to have little cytotoxic action even at the highest doses. Misonidazole was tested against hypoxic cultures from one tumour and produced complete suppression of leucine incorporation in all doses above 125 μg/ml.

It is concluded that some tumours contain cells which can survive prolonged periods of hypoxia. These cells may be killed by misonidazole but metronidazole appears ineffective.

41. *In vitro* production of lysozyme from monocytes of breast cancer patients: a new prognostic index?

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The monocyte/macrophage series has been implicated in the host response to cancer. These cells actively secrete lysozyme so that serum levels of this enzyme may indirectly reflect the activation of the system in tumour-bearing patients. However, serum lysozyme as a prognostic marker is probably too non-specific to be of clinical value (Chare et al., 1978). It was therefore decided to assess the activity of circulating monocytes from breast cancer patients by estimating the rate of *in vitro* lysozyme production according to the method of Gordon et al. (1974). Thirty patients with various stages of breast cancer before treatment were compared with 10 age-matched controls. Two

Patient group	Mean *in vitro* lysozyme production* No.	Mean±s.d.
A Healthy controls	10	0·12±0·06
B 'Operable' breast cancer (stages I and II)	12	0·61±0·26
C Stage III breast cancer	9	1·17±0·34
D Stage IV breast cancer	9	1·30±0·59

* μg ml^{-1} 2×100^{-6} mononuclear cells 24 h^{-1}

A *v.* B, $P<0{\cdot}001$ B *v.* C, $P<0{\cdot}001$

A *v.* C, $P<0{\cdot}001$ B *v.* D, $P<0{\cdot}01$

A *v.* D, $P<0{\cdot}001$ C *v.* D, n.s.

$\times 10^6$ mononuclear cells from the peripheral blood were cultured for three sequential 24-h periods for each subject and the average rate of production of lysozyme was calculated.

There was a highly significant increase in lysozyme production from the mononuclear cells of all groups of breast cancer patients compared with controls. Furthermore *in vitro* lysozyme production was significantly greater in the more advanced cases compared with the 'operable' group.

These results suggest that the degree of 'activation' of the peripheral blood monocytes may reflect the tumour burden of the host and provide a marker of prognostic value.

CHARE M. J. B., FORTT R. W., and BAUM M. (1978) Serum and tissue lysozyme in relation to pathological indices of prognosis in patients with breast cancer. British Association of Surgical Oncology, Cardiff.

GORDON S., TODD J. and COHN Z. (1974) *In vitro* synthesis and secretion of lysozyme by mononuclear phagocytes. *J. Exp. Med.* 139, 1228.

42. The protective effect of jejuno-ileal bypass in experimental intestinal cancer

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Subtotal small bowel bypass for obesity might increase the risk of subsequent intestinal cancer either in the atrophic excluded segment, as in Crohn's disease (Greenstein et al., 1978), or in the hyperplastic functioning segment, as after partial enterectomy (Williamson et al., 1978). This possibility was tested in rats ($n = 100$) weighing 110–140 g and receiving 6 weekly subcutaneous injections of azoxymethane (15 mg kg^{-1} wk^{-1}), starting 1 week after operation. Animals were randomized to receive 85–90 per cent jejuno-ileal bypass or resection, or no operation (controls).

At sacrifice 36 weeks postoperatively, mean body weight after bypass was 62 per cent and after resection 80 per cent of control values ($P < 0{\cdot}001$). Adaptation following bypass or resection was manifested by 18–82 per cent increments in villus height and crypt depth in the residual functioning small bowel ($P < 0{\cdot}05$); the depth of colonic crypts was unchanged, however. There were fewer rats with intestinal tumours after bypass (36 per cent) than after either resection (80 per cent) or no operation (91 per cent) ($P < 0{\cdot}005$). Bypass reduced the mean number of colonic tumours per rat from 1·36 to 0·32 ($P < 0{\cdot}001$). Although resection did not affect colonic tumour yield, it trebled the incidence of tumours in the duodenum and jejunum ($P < 0{\cdot}02$) and caused more anastomotic tumours than bypass.

The lower tumour incidence after jejuno-ileal bypass contrasts with enhanced carcinogenesis after equivalent resection. Profound reduction in body weight appears to prevent the promotional effect of adaptive hyperplasia.

GREENSTEIN A. J., SACHAR D., PUCILLO A. et al. (1978) Cancer in Crohn's disease after diversionary surgery. A report of seven carcinomas occurring in excluded bowel. *Am. J. Surg.* 135, 86–90.

WILLIAMSON R. C. N., BAUER F. L. R., OSCARSON J. E. A. et al. (1978) Promotion of azoxymethane-induced colonic neoplasia by resection of the proximal small bowel. *Cancer Res.* 38, 3212–3217.

43. Randomized controlled trial of vancomycin for postoperative diarrhoea and pseudomembranous colitis

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Pseudomembranous colitis is caused by toxigenic strains of *Clostridium difficile* which are usually resistant to most antimicrobials except metronidazole and vancomycin (Bartlett et al., 1978). Metronidazole is rapidly absorbed, whereas vancomycin achieves high concentration in the colon and may be useful for therapy (Tedesco et al., 1978).

All patients developing diarrhoea after major intestinal operation since April 1978 have been admitted to a prospective randomized double-blind trial ($n = 44$). Patients received oral vancomycin 125 mg 6-hourly for 5 days ($n = 22$) or an identical placebo ($n = 22$). Sigmoidoscopy and rectal biopsy were performed before and 5 days after entry to the trial. Stool samples were collected on days 1, 3 and 5 for identification of toxins and *C. difficile*, and on days 2 and 4 for vancomycin assay.

Sixteen patients had toxigenic strains of *C. difficile* characteristic of pseudomembranous colitis (vancomycin, 9; placebo, 7). On the fifth day of therapy only one patient receiving vancomycin had evidence of toxins of *C. difficile* in the stool compared with six controls ($P < 0{\cdot}05$). Vancomycin completely controlled diarrhoea in all except one patient with pseudomembranous colitis compared with persistent symptoms in all except one of the controls. Vancomycin had no influence in patients without pseudomembranous colitis. In pseudomembranous colitis elimination of toxin-producing *C. difficile* from the colon by vancomycin was associated with rapid clinical improvement.

BARTLETT J. G., CHANG T. W., GARWITH M. et al. (1978) Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *N. Engl. J. Med.* 298, 531–534.

TEDESCO F., MARKHAM R., GURWITH M. et al. (1978) Oral vancomycin for antibiotic-associated pseudomembranous colitis. *Lancet* 2, 226–229.

44. An electrophysiological study of the anal reflex in idiopathic faecal incontinence

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Histological studies have indicated that denervation of the external anal sphincter and puborectalis muscles occurs in many patients with iodipathic faecal incontinence (Parks et al., 1977). If a localized injury to the pudendal nerves is responsible then it should be possible to test this suggestion by demonstrating delayed conduction in these nerves.

We have attempted this indirectly by recording the motor-unit action potential associated with the anal reflex, of which both the sensory and motor components are conducted by the pudendal nerves (Frenckner and Van Euler, 1975). The latency and amplitude of the anal reflex was determined in a group of 33 normal subjects (aged 21–72, mean 47·7 years) comparing the results with those obtained from a group of 24 patients (aged 12–71, mean 46·5 years) with idiopathic faecal incontinence.

The results are as follows:

Reflex latency	*Range (ms)*	*Mean ± s.e. mean*	
Normal	5·0–11·25	8·3 ± 0·3	$P = 0{\cdot}001$
Incontinent	6·5–22·0	13·0 ± 0·8	(Mann–Whitney U test)

Reflex amplitude	*Range (mV)*	*Mean ± s.e. mean*	
Normal	20–350	100·9 ± 15·9	$P = 0{\cdot}001$
Incontinent	10–100	38·8 ± 5·8	(Mann–Whitney U test)

No reflex could be identified in one normal subject and the reflex was absent in 3 patients with faecal incontinence.

We consider these results provide strong evidence to support the concept that faecal incontinence in some patients results from pudendal nerve damage.

FRENCKNER B. and VAN EULER C. (1975) The influence of pudendal block on the function of the anal sphincters. *Gut* 16, 482–489.

PARKS A. G., SWASH M. and URICH H. (1977) Sphincter denervation in anorectal incontinence and rectal prolapse. *Gut* 18, 656–665.

45. Inhibition of the interdigestive myoelectric complex and lipid absorption: experimental study in the dog

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During fasting, the myoelectrical activity of the small intestine is characterized by the interdigestive myoelectric complex that recurs every 80–110 min in the dog. Feeding inhibits the myoelectric complex. The duration of inhibition of the myoelectric complex (DIMC) depends on the nature of food components (Hellemans et al., 1977). The purpose of this work was to study the variations of DIMC after ingestion of lipids associated with duodenal bypass, and to correlate them with the eventual alteration of intestinal absorption.

Six dogs were prepared with duodenal and jejunal cannulas and 3 dogs had a terminal ileostomy. Lipid at doses of 7·5 and 15 kcal/kg were alternatively given via the two cannulas. DIMC was determined from serosal jejunal electrodes. Absorption was determined by the measurement of lipid in the ileostomy output. The effect of bile (30 ml) introduced through the jejunal cannula was investigated.

Lipid	Route	DIMC (min)	Absorption (%)
7·5 kcal/kg	D	255±8	95±1
	J	211±7*	80±2*
	J+B	330±8*	100†
15 kcal/kg	D	447±7	75±2
	J	256±6*	50±3*
	J+B	450±7	70±3

D, duodenal; J, jejunal; J+B, jejunal +bile.
All results are mean±s.e. mean.
* Values significantly different from D.
† In each experience.

These results demonstrate that a defect of lipid absorption is associated with significant reduction of DIMC. Return of DIMC and the percentage absorption towards normal values was obtained by the addition of bile. These results suggest that a close relationship between DIMC and intestinal absorption of lipid might exist.

HELLEMANS J., VANTRAPPEN G., EECKHOUT C. et al. (1977) Inhibition of the interdigestive myoelectric complex in dogs by commercial food, proteins, carbohydrates, fat and MCT. *Gastroenterology* **72**, 1160.

46. Faecal bile acids and clostridia in the aetiology of colorectal cancer

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Hill et al. (1975) have reported an increased bile-acid concentration in association with nuclear dehydrogenating clostridia (NDC) in the faeces of colorectal cancer patients. This finding has not been confirmed and its importance in the aetiology of colorectal cancer remains unclear. We have studied 34 patients with colorectal cancer and 28 control patients with no known gastrointestinal disease. Stool specimens were obtained for biochemical analysis (total faecal bile acid, lithocholic acid, deoxycholic acid and cholic acid) and NDC isolation. A dietary history was taken from 30 colorectal cancer patients.

The mean total faecal bile-acid concentration (μmol/g) in the control group was 20±11 (mean±s.d.), significantly higher ($P<0·001$) than in the colorectal cancer group. No statistically significant difference was found between the two groups in either the concentration or the percentage distribution of the individual faecal bile acids measured. NDC were isolated from 69 per cent of colorectal cancer patients and 44 per cent of control patients, this difference not reaching statistical significance. Dietary history analysis failed to reveal significant increases in fat or protein intake in the colorectal cancer patients.

These results do not support the findings of Hill et al. and indicate that any relationship between faecal bile acids, bacteria and colorectal cancer requires further evaluation.

HILL M. J., DRASAR B. S., WILLIAMS R. E. O. et al. (1975) Faecal bile acids and clostridia in patients with cancer of the large bowel. *Lancet* **1**, 535–539.

47. Re-examination of the amylase to creatinine clearance ratio (ACCR) in acute pancreatitis

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It has been suggested that the ACCR is both a reliable and simple index of the presence of acute pancreatitis (Murray and Mackay, 1977) and that the test has a high degree of specificity for this disease (Warshaw and Fuller, 1975). Quite recently certain doubts have been expressed about these claims, and the place of the test in the diagnosis of acute pancreatitis (Lankisch et al., 1977). The present study comprised 86 patients with primary acute pancreatitis (mean admission serum amylase 5900 U/l). Whether an ACCR of 3 per cent or 5·3 per cent is considered the upper limit of normal, a significant proportion of results were in the normal range for day 1 through to day 5 of illness (Table). Indeed, of the 12 patients with the highest serum amylase values, a mean ACCR of 4·6 per cent was found on the first day of illness and 7 of these had an ACCR of less than 3 per cent. Comparison with other parameters revealed significantly fewer diagnostic levels of ACCR than serum or urine amylase alone, or the ratio of urinary amylase to urinary creatinine on day 1, and no advantage for ACCR as a test later in the illness. Both the specificity and reliability of this test must be seriously questioned.

'Normal' ACCR results (%)

	Day 1	2	3	4	5
ACCR					
<3%	41	53	49	35	50
<5·3%	66	82	76	81	91

LANKISCH P. G., KOOP H., OTTO J. et al. (1977) Specificity of increased amylase to creatinine clearance ratio in acute pancreatitis. *Digestion* **16**, 160–164.

MURRAY W. R. and MACKAY C. (1977) The amylase creatinine clearance ratio in acute pancreatitis. *Br. J. Surg.* **64**, 189–191.

WARSHAW A. L. and FULLER A. F. (1975) Specificity of increased renal clearance of amylase in the diagnosis of acute pancreatitis. *N. Engl. J. Med.* **292**, 325–328.

48. The effect of gastric distension on the canine gastric basal electrical rhythm (BER)

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Slowing of the frequency of the gastric basal electrical rhythm (BER) before and after vagotomy has been observed during gastric distension (Nelson et al., 1967; Kelly and Code, 1969). The effect of gastric distension on the BER was analysed on 13 isolated canine stomach preparations. Distension produced an immediate change of the BER rate, which returned to the fasting level after emptying of the stomach. In 73 studies a decrease in the frequency occurred in 67 per cent, an increase in 27 per cent and no change in 6 per cent.

Secondly, the response of the gastric BER to distension was measured on three conscious dogs before (12 studies) and after (12 studies) truncal vagotomy. Whereas both liquid and solid meals caused a similar immediate slowing of the BER rate of 20 per cent, recovery to the fasting level within 30 min was only seen after the liquid meals. Although less pronounced the gastric response to distension was preserved after vagotomy in two animals. In the third animal (with gastric retention) the BER remained irregular throughout fasting and feeding.

It is concluded that (*a*) although the isolated preparations suggest a local muscle response, the direction of the response may be dictated by extrinsic nerves; (*b*) persistence of the response after vagotomy suggests a neural controlling mechanism independent of the central vagus.

KELLY K. A. and CODE C. F. (1969) Effect of transthoracic vagotomy on canine gastric electrical activity. *Gastroenterology* **57**, 51–58.

NELSON T. S., EIGENBRODT E. H., KEOSHIAN L. A. et al. (1976) Alterations in muscular and electrical activity of the stomach following vagotomy. *Arch. Surg.* **94**, 821–835.

49. Experimental studies of small-diameter arterial prostheses

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A total of 150 graft experiments has been performed in the canine carotid artery to compare the 5–6-hour thrombotic threshold velocity (TTV), the flow surface index (FSI) and the 1-week patency rates of prostheses 6 cm long and 3–4 mm in diameter of different materials and wall configurations. Prostheses studied were crimped and non-crimped porous Dacrón fabric (USCI Sauvage filamentous vascular prosthesis), expanded polytetrafluoroethylene (Gore-Tex) and glutaraldehyde-processed human umbilical vein (Meadox Biograft). These studies show important differences among these grafts (Table).

Graft	TTV (cm/s)	FSI 5–6 h	FSI 1 wk	1-wk patency
USCI Sauvage non-crimped	5–6	99	98	83%
Gore-Tex	5–6	85	98	80%
USCI Sauvage crimped	6–6·5	75	98	62·5%
Meadox Biograft	12–15	5	38	60%

These implantations in the canine carotid artery indicate that a properly pre-clotted, non-crimped, porous fabric prosthesis (autogenous fibrin flow surface) is substantially better than the Meadow Biograft. In contrast, the Gore-Tex prosthesis is comparable to a properly pre-clotted, non-crimped, porous fabric Dacron prosthesis.

On this basis, a non-crimped porous fabric Dacron prosthesis that has both the surgical advantages of crimping and the rheologic attributes of a smooth flow surface has been developed.

50. Postoperative changes in red blood cell deformability

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Red blood cell deformability is known to influence blood flow through the microcirculation and may also be important in determining flow rates through larger vessels. Red cell deformability has been shown to be impaired in patients with peripheral vascular disease (Reid et al., 1976) and patients with diabetes (Barnes et al., 1977).

To measure red blood cell deformability, we have modified our earlier filtration technique and used a 5 per cent concentration of erythrocytes resuspended in their own plasma, which is then passed through a nucleopore filter with pore size of 5 μm diameter.

We have shown that patients undergoing major reconstructive surgery have a fall in red cell deformability to 50 per cent of preoperative values. This fall is maximal at 24–48 h and returns to preoperative values after 5–10 days. We have investigated the cause of this change by studying deformability in patients undergoing non-arterial operations without blood transfusion and in patients having operations under general anaesthetic but minimal surgical stress (cystoscopy). Patients having non-urgent transfusion for anaemia were also studied, and measurements were made in 30 patients in all. The only patients in whom deformability changed were those subject to surgical stress. We believe that this postoperative change may contribute to early failures of arterial surgery, and may predispose to deep vein thrombosis.

BARNES A. J., LOCK P., SCUDDER P. R. et al. (1977) Is hyperviscosity a treatable component of diabetic microcirculatory disease? *Lancet* **2**, 789–791.

REID H. L., DORMANDY J. A., BARNES A. J. et al. (1976) Impaired red cell deformability in peripheral vascular disease. *Lancet* **1**, 666.

51. Porcine dermis therapy for varicose ulcers

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A pilot study suggested that lyophilized partial-thickness pigskin dressings (Corethium II, Ethicon Ltd) could accelerate the healing of varicose and traumatic leg ulcers (Rundle et al., 1976).

A clinical trial was undertaken to compare this material with 'Bisgaard' therapy as standardized in our hospital in recent years using paste-impregnated bandages (Seton Products Ltd), elastic compression and physiotherapy. Twenty-six ambulant outpatients were randomly allocated to treatment or control groups. Patients with multiple ulcers received only one form of treatment.

	Bisgaard ($n = 11$)	Porcine ($n = 15$)
Age (yr)	56–80 (mean 70·6)	45–88 (mean 64·1)
No. of ulcers	17	22
Surface area (cm^2)	0·47–16·43 (mean 3·83)	23–47·85 (mean 8·01)
Duration of healing	3–63 wk (mean 13·1)	1–16 wk (mean 7·0)

In 3 patients (1 Bisgaard, 20 porcine) the ulcers failed to heal and they required inpatient treatment. Comparison of healing rates showed a mean for the Bisgaard treated ulcers of 7·7 weeks per $\sqrt{(\text{area})}$ versus 4·7 weeks for the porcine group. The improvement in healing rate was statistically significant.

RUNDLE J. S. H., CAMERON S. H. and RUCKLEY C. V. (1976) New porcine dressing for varicose and traumatic leg ulcers. *Br. Med. J.* **2**, 216.

52. Assessment of treatment in Raynaud's phenomenon by Doppler ultrasound velocimetry

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Little information is available about the state of digital vessel patency in patients with Raynaud's phenomenon unless arteriography, with its potential hazards, has been performed. Now, using a safer method—directional Doppler velocimetry—vessel patency can be estimated along the length of the finger. Digital vessel systolic pressure can also be measured accurately by inflating a plastic cuff, placed around the proximal phalange, above systolic pressure, and then listening to the returning arterial flow, on cuff deflation, with a Doppler probe.

Twenty-six patients with Raynaud's phenomenon were randomly allocated to 3 treatment groups—placebo, systemic heparinization (5000 i.u. i.v.) once weekly for 4 weeks and plasmapheresis once weekly for 4 weeks. The total weekly plasma exchange was 2·5 l. Digital vessel patency and pressures were assessed before treatment, after treatment and at 6-month follow-up. Assessment was performed at 20±0·5 °C and after hand immersion in water at 15 °C and 45 °C.

Plasmapheresis produced a significant ($P<0·05$) improvement in vessel patency and in digital blood pressure ($P<0·02$) at 20±0·5 °C and at 15 °C as assessed by Doppler techniques. Whole blood viscosity, at high shear rates (91 s^{-1}) was significantly reduced ($P<0·01$) in the plasmapheresis group, but in no other.

Thus, plasmapheresis is an effective form of treatment in severe Raynaud's phenomenon.

53. Evaluation of a pulsed Doppler imaging system in peripheral vascular disease

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A directional 30-channel 5 MHz pulsed Doppler artery and vein imaging system (MAVIS, GEC Medical) was used to detect (*a*) progressive narrowing in synthetic arterial grafts and (*b*) stenosis at the origin of the profunda femoris artery. Longitudinal and transverse vessel images were obtained: in addition, each of the 30 channels was selected in turn to obtain the velocity wave forms and hence the velocity profile of the moving stream of blood. The channel with the maximum velocity wave form was recorded above and below arterial stenoses to demonstrate loss of pulsatility and wave form damping.

In a follow-up study of patent 10-mm Dacron grafts, 128 scans of 32 limbs were performed. The ultrasound images of these grafts were satisfactory and reproducible. The internal diameter of long iliopopliteal grafts did not change from groin to mid-thigh level, but decreased from 7·84±0·36 mm (mean ±s.e. mean) at mid-thigh level to 6·31±0·44 mm at popliteal level, indicating distal graft stenosis ($P<0{\cdot}005$, Wilcoxon). Damping of the maximum velocity time wave form was also demonstrated in these long grafts. No distal narrowing was found in 14 short grafts (10 aortofemoral, 4 iliofemoral), but in 3 the femoral anastomosis was dilated. In 3 grafts localized but haemodynamically insignificant stenoses were detected.

Mapping of blood flow at the bifurcation of the common femoral artery was performed in 14 patients with chronic ischaemia. The vessel images compared poorly with arteriograms, but severe damping of the maximum velocity time wave forms across the profunda femoris ostium was demonstrated, indicating the presence of haemodynamically significant profunda orifice stenosis (damping factor>1·57).

These results suggest that the anatomical and functional information obtained with MAVIS can together be used in the non-invasive detection of luminal narrowing of Dacron arterial grafts and in the preoperative assessment of arterial disease.

54. The relationship between ultrasonic pulsatility index and proximal arterial stenosis

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Although the pulsatility index (PI), derived from spectral analysis of ultrasonic Doppler signals, is claimed to assess accurately arterial inflow (Gosling, 1972; Charlesworth et al., 1975), the relationship between proximal arterial stenosis and PI has not been fully evaluated.

In a series of canine experiments over 200 measurements of pressure, flow (using an indwelling electromagnetic flowmeter) and PI were made distal to implanted arterial stenoses of varying length (5–9 mm) and cross-sectional area (36–94 per cent reduction in area). These measurements indicate:

1. The PI correlates broadly with severity of stenosis but for individual stenoses the scatter was wide.
2. For stenoses of up to 75 per cent reduction in area the PI varied between 1 and 7; only when the stenosis was greater than 90 per cent was the PI invariably low (between 0·25 and 2).
3. For a given stenosis the PI correlated with peripheral resistance. The dependence of the PI on peripheral resistance was much greater for stenoses of less than 75 per cent reduction in area than for the tighter stenoses.

It seems that the PI is influenced both by inflow and by the resistance of the vessels distal to the stenosis. In this canine model, the PI could not predict the adequacy of arterial inflow.

CHARLESWORTH D., HARRIS P. L., CAVE F. D. et al. (1975) Undetected aorto-iliac insufficiency: a reason for early failure of saphenous vein bypass grafts for obstruction of the superficial femoral artery. *Br. J. Surg.* **62**, 567–570.

GOSLING R. G. (1972) In: ROBERTS V. C. (ed.) *Blood Flow Measurement*. London, Sector.

55. The influence of aortofemoral Dacron bypass grafts on platelet and fibrinogen kinetics

C. N. MCCOLLUM, S. M. RAJAH, M. D. PEPPER, P. A. LEAROYD and R. C. KESTER, *University Department of Surgery, St James's University Hospital, and Regional Blood Transfusion Centre, Leeds*

Occlusion of an arterial graft results partly from the thrombogenic effects of its luminal surface. Dacron aortofemoral grafts rarely thrombose because of wide graft diameter and rapid blood flow, but results in small grafts are less satisfactory so that antithrombotic therapy may be indicated. The duration of such therapy should be based on the 'thrombogenic period' in graft maturation.

To evaluate this period, platelet and fibrinogen kinetics, using ^{51}Cr and ^{125}I respectively, were measured preoperatively and at 3, 6 and 9 months in 10 patients after aortofemoral Dacron bypass. Six age-matched volunteers were similarly studied.

	Control	Preop.	3 mth	6 mth	9 mth
Platelet survival (d)	8·5	8·8	7·6	7·9	8·4
Platelet turnover ($\times 10^3$/d)	34	39	47	39	30
Fibrinogen $T_{\frac{1}{2}}$ (d)	4·1	3·7	3·4	4·0	4·0
Fibrinogen fractional catabolic rate	0·26	0·27	0·35	0·29	0·27

Platelet survival time was reduced ($P<0{\cdot}01$) and platelet turnover increased at 3 months postoperatively compared with preoperative levels. Similarly, fibrinogen $T_{\frac{1}{2}}$ was decreased, and fractional catabolic rate increased at 3 months ($P<0{\cdot}01$). These indices of thrombogenic activity returned to preoperative levels by 9 months. Preoperative platelet and fibrinogen consumption in patients tended to be higher than in volunteers.

We suggest that Dacron aortofemoral grafts remain thrombogenically active for about 9 months. Where blood flow conditions are suboptimal or graft diameters are small, it may be prudent to use antithrombotic therapy to protect patency.

56. Anti-thrombotic therapy for vascular prostheses: an experimental model evaluating aspirin and dipyridamole

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Although Dacron is widely used in the construction of arterial prostheses, the fabric has been shown to be relatively thrombogenic (Hamlin et al., 1978). We have investigated the effect of acetysalicylic acid (ASA), dipyridamole (DPM) and combinations of these drugs on the response of platelets to woven Dacron perfused in an artificial circulation.

These circuits were perfused by heparinized blood donated by 6 volunteers after each had taken: (1) no drugs; (2) ASA 300 mg t.d.s., (3) DPM 100 mg q.i.d., (4) ASA 300 mg+DPM 75 mg combined t.d.s.; (5) ASA 80 mg+DPM 75 mg combined t.d.s., separately for 1 week (each treatment separated by 2 weeks). Bleeding times were performed before each donation. Platelet count, adhesion and aggregation were estimated through perfusion. Each graft's surface was examined by scanning electron microscopy at the end of perfusion.

	Mean reduction during perfusion P. c. (%)	P. ag. (%)	P. ad. (%)	Mean no. platelets adherent to Dacron	Mean bleeding time (min)
1	17·2	16·9	11·3	251	5·15
2	8·1*	−2·1*	7·5	73*	10·6*
3	15·8	3·9	7·66*	145*	6·2
4	11·8	−12·6*	0·33*	72*	11*
5	7·7*	−10·5*	6·5*	80*	7·6*

P.c., platelet count; P. ag., platelet aggregation; P. ad., platelet adhesion.
* $P<0{\cdot}05$ compared with control (group 1) value (Wilcoxon signed rank test).

ASA was more effective than DPM, significantly impairing function and reducing consumption of platelets by Dacron, but prolonging the bleeding time. Inhibition of platelet function and platelet adherence to Dacron by low dose ASA+DPM was similar to that achieved by ASA alone and larger dose ASA+DPM, the bleeding time being less extended. We suggest that ASA in low dose plus DPM may favourably influence the thrombogenic response of flowing blood to Dacron with less risk of bleeding.

HAMLIN G. W., RAJAH S. M., CROW M. J. et al. (1978) Evaluation of the thrombogenic potential of three types of arterial graft. *Br. J. Surg.* **65**, 272–276.

57. Suppressor cells in immunological enhancement

W. S. HENDRY and N. L. TILNEY, *Departments of Surgery, Aberdeen University and Harvard University (Peter Bent Brigham)*

The survival of (LEW×BN) F_1 cardiac allografts can be significantly prolonged in LEW hosts by combining active and passive enhancement (Tilney et al., 1978). The role of suppressor cells in immunological enhancement was tested *in vivo*, transferring thymus cells from enhanced rats bearing well-functioning grafts to syngeneic recipients of test cardiac allografts. Six days after transplantation, 10^8 thymocytes were transferred to virgin LEW rats given a (LEW×BN) F_1 cardiac allograft 24 h later. The mean survival time of test grafts was 14±3 days and 6·4±1 days following transfer from enhanced and unmodified LEW hosts respectively ($P<0\cdot001$). The transfer of 10^6, 10^7 and 5×10^8 thymocytes from enhanced rats 6 days post transplant gave test graft survival of 8±1·5 days, 7·5±0·5 days and 8±1 days respectively (n.s.).

When 10^8 thymocytes were harvested from enhanced hosts 3, 9 or 12 days post transplant, test allograft mean survival times were 7·4±1 days, 9±1 days ($P<0\cdot005$) and 7·4±0·5 days, respectively. Specificity was tested by the survival of third party allografts. Following transfer of 10^8 thymocytes 6 days post transplant, the mean survival time (LEW×Wi Fu) F_1 allografts was 7±1 days (n.s.). Passive transfer of serum from enhanced animals 6 days post transplant did not prolong test graft survival (mean survival time = 7·5±1 days).

Suppressor cells participate in the maintenance of enhancement, the phenomenon being highly specific and time- and dose-restricted.

TILNEY N. L., BANCEWICZ J., ROWINSKI W. et al. (1978) Enhancement of cardiac allografts in rats. Comparison of host responses to different treatment protocols. *Transplantation* **25**, 1–6.

58. The effect of immunization and route of administration on the anti-tumour action of pig mononuclear cells

TERESA LAI and SARAH PRICHARD-THOMAS, *Department of Surgery, University of Bristol*

Cells from pig mesenteric lymph nodes were used to treat mouse mammary tumours. Two models were employed.

In the first 1×10^5 tumour cells were injected intravenously on day 0 into isogenic mice to produce pulmonary tumours. The mice received 200 rad thoracic irradiation on day 3 and 20×10^6 pig mononuclear cells on day 7. The pig cells were either non-immune or tumour-immune. They were injected intravenously to make contact with the tumours in the lung. Only immune (I) pig cells, injected intravenously, reduced the number of pulmonary tumour nodules on day 14.

Category	Median no. of pulmonary tumours	Significance Un.	Significance Irr.	
Untreated ($n=6$)	20·0		n.s.	
Irradiation ($n=12$)	14·0	n.s.		
Irradiation+non-I cells i.v. ($n=4$)	23·5	n.s.	n.s.	
Irradiation+I cells i.v. ($n=8$)	5·5	<0·001	<0·02	$P<0\cdot005$
Irradiation+I cells i.p. ($n=8$)	15·0	n.s.	n.s.	

Un,, untreated; Irr,, irradiated.

In the second model 1×10^6 tumour cells were injected intraperitoneally on day 0 to produce multiple peritoneal tumours in isogenic mice. Pig mononuclear cells, 40×10^6 non-immune or tumour-immune, were injected on day 7. Only immune pig cells injected intraperitoneally were effective in prolonging the survival of the mice.

Category	Mean survival time (d)	Significance*	
Untreated ($n=7$)	29·9		
Non-I pig cells i.p. ($n=7$)	33·0	n.s.	
I pig cells i.p. ($n=8$)	44·6	$P<0\cdot02$	$P<0\cdot05$
I pig cells i.v. ($n=7$)	31·0	n.s.	

* Significance from untreated.

Thus, to obtain an anti-tumour effect, pig cells must be tumour-immune and make contact with the tumours.

59. Prolongation of murine skin allografts across a major histoincompatibility locus using supernatants from Concanavalin-A-activated spleen cells

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Supernatants from Concanavalin-A (Con-A)-activated spleen cell cultures (CONS) have been found to suppress the responses of laboratory mice to challenge with heterologous erythrocytes (Reinertsen and Steinberg, 1977). This may possibly be mediated by the stimulation of suppressor T-lymphocytes (Tadakuma and Pierce, 1978). We therefore decided to explore the possibility that CONS might delay the rejection of allografts across a major histoincompatibility locus. CONS and control supernatants were prepared from 48-h cultures of BALB/c splenocytes. Con-A was removed from all the supernatants with Sephadex G-75. Three groups of BALB/c mice were injected intraperitoneally with 1 ml twice daily for 5 days with either CONS, control supernatant or isotonic saline. Skin grafts from donor C3H mice were performed on all the injected mice either on the day of first injection (day 0) or 24 h after the first injection (day −1). Using standard criteria the day upon which graft rejection occurred was determined. The results were as follows:

	Mean day of rejection (±s.d.)
Control supernatants ($n=11$)	10·5±1·25
Saline ($n=23$)	11·1±1 3
CONS ($n=23$)	14 6±1·8

The mean time of rejection following injection of CONS was significantly longer than both that of the saline control group ($t=7\cdot6$, $P<0\cdot001$) and the control supernatant group ($t=6\cdot27$, $P<0\cdot001$). Further analysis of these results reveals that skin grafts in animals whose injections of CONS commenced on day 0 ($n=11$) survived 15·4±1 9 days whereas those whose injections commenced on day −1 ($n=12$) survived 13·8±1·3 days, though this just failed to reach statistical significance ($r=99\cdot2$).

It is concluded that supernatants from Con-A-activated spleen cells do contain a factor which can defer allograft rejection.

REINERTSEN J. L. and STEINBERG A. D. (1977) *In vivo* immune response suppression by the supernatant from Concanavalin-A-activated spleen cells. *J. Immunol.* **119**, 217–222.
TADAKUMA T. and PIERCE C. W. (1978) Mode of action of a soluble immune response suppressor (SIRS) produced by Concanavalin-A-activated spleen cells. *J. Immunol.* **120**, 481–486.

60. The predictive value of pre-transplant mixed lymphocyte reaction in renal transplantation: a prospective 5-year study

B. K. SHENTON, G. PROUD and R. M. R. TAYLOR, *Department of Surgery, Royal Victoria Infirmary, Newcastle upon Tyne*

A correlation between the outcome of cadaver kidney transplants and the strength of stimulation obtained between recipient and donor cells in the two-way mixed lymphocyte reaction has been described (Opelz and Terasaki, 1977). However, the conventional 5-day test is not suitable for prospective matching in cadaver transplantation. The aim of the present investigation was to evaluate donor×recipient mixed lymphocyte reaction prospectively in a series of 72 consecutive renal transplants (from January 1971 to November 1972) using a 3-h *in vitro* technique. Graft survival was assessed independently at 5 years. Mixed lymphocyte reactions were measured in the macrophage electrophoretic mobility (MEM) test (Shenton et al., 1975). Two groups were considered, based on the recommendation of Cochrum et al. (1973): (*a*) stimulation indices (SI) up to 8 per cent; and (*b*) SIs above 8 per cent.

Actuarial graft survivals for all patients are shown in the Table, which gives the percentage graft survival.

	SI	
	0–8% ($n = 33$)	8 1–16·1% ($n = 27$)
0·5 yr	91	63 4
1 yr	75·5	50·7
2 yr	75·5	38
3 yr	65	38
4 yr	59	34·5
5 yr	59	21·6

Five-year graft survival was significantly greater ($P<0\ 01$) in the low (<8 per cent) SI group. Prior blood transfusion combined with an SI of less than 8 per cent gave the best graft survival (80 per cent at 6 years).

In conclusion, low SIs are associated with better 5-year graft survival (59 per cent) than high SIs (21·6 per cent). The assessment of the mixed lymphocyte reactions in the MEM test may allow more precise selection of recipients for transplantation and the test described is of clinical relevance since it may be completed in 3 h.

COCHRUM K. C., PERBINS H. A., PAYNE R. O. et al. (1973) The correlation of MLC with graft survival. *Transplant Proc.* **5**, 391–396.

OPELZ G. and TERASAKI P. I. (1977) Significance of mixed leukocyte culture testing in cadaver kidney transplantations. *Transplantation* **23**, 375–380.

SHENTON B. K., ULDALL P. R., SWINNEY J. et al. (1975) Assessment of histocompatibility by mixed lymphocyte reaction as measured by the MEM test. *Tissue Antigens* **5**, 246–256.

61. Timing of blood transfusions before organ transplantation

G. PROUD, B. K. SHENTON, P. S. VEITCH and R. M. R. TAYLOR, *University Department of Surgery, Royal Victoria Infirmary, Newcastle upon Tyne*

The benefits of previous blood transfusions on kidney transplant survival are becoming increasingly recognized. However, it is unknown if the timing of the transfusions is important. This was studied in the inbred rat cardiac allograft model using the following unrelated strains: (i) heart donor, PVG/C (AgB5); (ii) blood donor, DA (AgB4); (iii) recipient, WAG (AgB2). Two 2-ml transfusions of DA whole blood were given to the recipient 3 days apart either 2 weeks (2/52) or 4 weeks (4/52) before transplantation. The experiment was repeated adding immunosuppression (IS) to the transfusion regimen—azathioprine 4 mg kg^{-1} d^{-1} and prednisolone 6 mg kg^{-1} d^{-1}, given intraperitoneally, commencing 1 h before transplantation.

Experimental groups	*n*	Median graft survival (d)
A Untreated control rats	17	7
B Immunosuppressed (IS) rats	8	9
C Transfused 4/52	9	9
D Transfused 2/52	9	9
E Transfused 4/52 plus IS	9	9
F Transfused 2/52 plus IS	9	22

Using the Wilcoxon rank sum test, rats of group A had significantly shorter graft survival times than any other group ($P<0\ 01$). Groups B, C, D and E did not differ from one another, but group F showed significant prolongation of graft survival over all other groups ($P<0{\cdot}01$).

Following transfusion alone (DA to WAG) there was a highly significant fall in the two-way mixed lymphocyte reaction (PVG/C × WAG), most evident between 2 and 3 weeks after transfusion, subsequently returning towards pretransfusion levels. There was a simultaneous rise in the ability of plasma following transfusions to inhibit the responses of sensitized lymphocytes to antigen.

Thus, transfusions given 2 weeks before transplantation were more beneficial to graft survival than those given 4 weeks before transplantation. This correlated with a fall in the mixed lymphocyte reaction, and a rise in the lymphocyte inhibitory activity of plasma. These observations may have implications in human clinical transplantation.

62. What is the correct dose of *Corynebacterium parvum*?

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This study in mice was designed to compare the effects of a single high dose (466 μg), single low dose (70 μg) or multiple low doses of intravenous *Corynebacterium parvum*. Multiple injections were given weekly for 6 weeks.

All treatments decreased body and thymus weights, increased spleen weight threefold and liver weight twofold. Changes were maximal at 2 weeks, reverting to normal within 5 weeks. Repeated treatments raised a higher titre of anti-*C. parvum* agglutinating antibodies than a single dose (26 $\log_2$ compared with 8 $\log_2$).

Single low dose *C parvum* given at the time of implantation of Lewis carcinoma, day 0, significantly decreased primary tumour growth and inhibited pulmonary metastases. Multiple treatments had no additional effect. Survival was significantly prolonged by a single low dose on day 7, but not when given on day 13. Repeated treatments gave no extra protection.

Pretreatment with multiple doses counteracted the anti-metastatic effect of *C. parvum* when given at the time of tumour implantation. Abrogation still occurred after treatment-free intervals of 50 days and 90 days.

We conclude from these studies that a single dose of 70 μg is effective against the Lewis lung tumour. Multiple doses are no more effective, and when given before tumour may inhibit the beneficial effects of *C. parvum*. The underlying mechanisms are under investigation.

63. Urinary β-thromboglobulin in venous thromboembolism

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β-Thromboglobulin is released from platelets during aggregation and may be a marker for venous thromboembolism. Plasma estimation of β-TG has been shown to be of limited clinical value (Smith et al., 1978). Is urine sampling of more value?

Plasma and urine samples were obtained from 7 patients with proved venous thrombosis and from 11 patients without evidence of thrombotic disease.

	DVT ($n = 7$)	No DVT ($n = 11$)	
Urine			
No. of samples	24	12	
Mean (μg/l)	1·4	0 19	$t = 6{\cdot}06$
Range (μg/l)	0·12–2 0	0 15–0·2	$P<0{\cdot}001$
Plasma			
No. of samples	10	12	
Mean (μg/l)	539	305	$t = 0{\cdot}6$
Range (μg/l)	16–4000	24–1725	$P>0{\cdot}5$

All patients with DVT showed elevated urinary levels of β-TG and only one patient had normal levels at any stage during the 2-day study period. All patients without DVT showed normal levels. The difference between the means was highly significant.

There was no difference in the plasma levels between the two groups. However, elevated urinary levels were also detected in patients without evidence of venous thrombosis up to 14 days after surgery—in one patient with a ruptured Baker's cyst and in one with cellulitis.

Urinary β-thromboglobulin assay appears to be a more valuable discriminant in venous thromboembolism than the plasma assay.

SMITH R. C., DUNCANSON J., RUCKLEY C. V. et al. (1978) Thromboglobulin and deep vein thrombosis. *Thromb. Haemostasis.* 39, 338–345.

64. The significance of the popliteal valve in relation to ambulatory venous pressure and ulceration

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Forty-two limbs (38 patients) who had had deep venous thrombosis (DVT) extending into the femoral or iliofemoral segment at least 5 years earlier and 10 limbs of 10 healthy volunteers were studied. The ambulatory venous pressure was measured by inserting a needle in a vein on the foot; the presence of reflux in the popliteal vein was determined by a directional Doppler ultrasonic blood velocity detector. All patients had ascending venography.

No. of limbs	IF or F segment	Popliteal valve	No. of limbs with ulceration	Mean AVP±s.d. (mmHg)
10	Normal	Competent	0	20±11
3	IF recan.	Competent	0	22±10
9	IF recan.	Incompetent	3	65±17
5	IF occ.	Competent	0	43±15
14	IF occ.	Incompetent	10	82±16
1	F recan.	Competent	0	24
3	F recan.	Incompetent	3	51±8
1	F occ.	Incompetent	1	70

F, Femoral; IF, iliofemoral; AVP, ambulatory venous pressure; recan., recanalization; occ., occlusion.

The results suggest that the most important factor in determining the ambulatory venous pressure and ulceration in post-phlebitic limbs is the condition of the popliteal valve. Ulceration does not occur even in the presence of occlusion if the popliteal valve is competent. The extent of DVT and recanalization or the failure of recanalization are of secondary importance.

65. Objective evaluation of speech after major oral surgery

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Speech was quantified using a word list of monosyllables of all the 19 English consonants, 24 consonant clusters and 21 vowels. The subjects read out each word from a card and a three-man jury wrote down what they heard. A score of one was given for a correct answer by each jury member. The discriminatory value of the resulting scores was calculated by the phi-index (Anderson, 1976), and on the basis of this a list was compiled of 50 words that were good discriminators, so that the maximum possible score was 150.

Forty-six patients who had undergone major oral surgery and 47 normal subjects were studied. The normal subjects' scores ranged from 100 to 146 (median 138). Since a minimum of 40 per cent of phonemes is required for intelligible speech, the scores can be divided as follows: 0–60 as unintelligible, 60–100 as intelligible but impaired and over 100 within the normal range. The results for the patients (Table) show that the two factors which render a patient unintelligible are ankylosis of the tip of the tongue and a soft palate defect. Pure loss of bulk is much less important. This result questions the value of replacement by a distant skin flap merely to replace bulk.

	Score		
	100–150	60–99	0–59
Loss of bulk	12	4	0
Ankylosis of tip of tongue	0	0	5
Soft palate defect	0	0	4

ANDERSON J. (1976) *The Multiple Choice Question in Medicine.* London, Pitman Medical.

66. Acute painless abdominal distension and lung infection

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It has been suggested that hypoxaemia following abdominal surgery is due to distension, pain and analgesics (Wahba et al., 1975). Good correlation exists between functional residual capacity (FRC), closing volume (CV) and arterial oxygenation (Nunn et al., 1978).

The purpose of this study was to investigate the effect of acute painless abdominal distension on CV and FRC. Five healthy volunteers underwent acute abdominal distension by instilling 3 l of Hartmann's solution into the stomach via a nasogastric tube over 1 h. FRC and CV were measured pre- and post-distension, using a helium dilution technique (Green and Travis, 1972). The results are shown in the Table.

	Subject				
	1	2	3	4	5
FRC (litres)					
Control	3·01	3·99	2·73	3·58	3·76
Post-distension	2·29	1·90	1·24	2·51	2·38
			$t = 5{\cdot}9$ $P < 0{\cdot}002$		
CV (litres)					
Control	0·500	0·660	0·490	0·600	0·650
Post-distension	0·775	1·100	0·600	0·850	1·100
			$t = 4{\cdot}8$ $P < 0{\cdot}005$		

This study has shown that acute painless abdominal distension causes significant respiratory dysfunction.

GREEN M. and TRAVIS D. M. (1972) A simplified closing volume method suitable for field use. *Lancet* 2, 905–906.

NUNN J. F., WILLIAM I. P., JONES J. G. et al. (1978) Detection and reversal of pulmonary absorption collapse. *Br. J. Anaesth.* 50, 91–99.

WAHBA W. M., DON H. F. and CRAIG D. B. (1975) Postoperative epidural analgesia: effects on lung volumes. *Can. Anaesth. Soc. J.* 22, 519–527.

67. The role of nodal disease in primary lymphoedema

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Primary lymphoedema is generally thought to be a disease of peripheral lymphatics and less consideration has been given to the role of lymph nodes in this process. Distal hypoplasia is associated with a good prognosis, but proximal obstructive hypoplasia is associated with a progressively severe form of lymphoedema.

The morphology of inguinal lymph nodes has been studied in 42 patients with primary lymphoedema and compared with inguinal nodes. One patient had Milroy's disease, two had megalymphatics and the rest had primary hypoplasia. In this last group 19 had distal hypoplasia, 11 had obstructive hypoplasia and 9 had a mixed lymphographic picture.

The histological findings are correlated with the lymphographic and clinical appearances in the different groups. There was a dense cortical fibrosis in the nodes of 12 patients (32 per cent) which was associated with obliteration of the adjoining afferent lymphatics. The process was unrelated to episodes of cellulitis or duration of disease. The severity of the nodal and clinical changes were related and 10 of the 12 patients with cortical fibrosis had swelling of the whole limb.

The results suggest that in patients with proximal obstruction on lymphography, the primary disease may be in the nodes and not in the peripheral vessels.

68. Do patients eat enough after colon surgery?

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Some patients after major surgery suffer from protein energy malnutrition. It is not known if the magnitude of the energy deficit is related to deficient food intake in the postoperative period.

We have studied voluntary food intake and energy balance in 6 male and 6 female patients over a 2-week period following elective colon surgery. Daily voluntary food intake was recorded by weighing all food consumed by the patient and home voluntary food intake was estimated by a dietary history technique. Energy balance was calculated from the voluntary food intake and from the changes in body fat and protein over the study period (Hill et al., 1978).

Eleven patients who had an uncomplicated recovery began to eat 2–7 days after the operation, reaching a maximum voluntary food intake between 7 and 14 days. The maximum voluntary food intake reached during this period was closely related to the home voluntary food intake ($r=0{\cdot}84$; $P<0{\cdot}01$).

There was no correlation between postoperative voluntary food intake and energy output over the study period. The higher the energy output, the more energy was derived from endogenous fat and protein. An average energy deficit of 1155 kcal per day (range +197 to −2758) was observed, and there was no significant relationship between this deficit and the voluntary food intake, which averaged 949 kcal per day (range +371 to +1833).

It is concluded that the amount of food consumed by patients postoperatively is determined by their previous home intake and not by their energy output. Patients with high energy outputs do not compensate by increasing voluntary food intake and large energy deficits can develop.

HILL G. L., MCCARTHY I. D., COLLINS J. P. et al. (1978) A new method for the rapid measurement of body composition in critically ill surgical patients. *Br. J. Surg.* **65**, 732–735.

Correspondence

Abdominal tuberculosis

Sir,

Please permit me to make a few belated comments on the article entitled 'Abdominal tuberculosis in the 1970s; a continuing problem' by Shukla and Hughes (*Br. J. Surg.* **65**, 403–405). In this paper the authors have drawn attention to the difficulties in making a diagnosis of abdominal tuberculosis using the standard methods.

Two diagnostic aids that may be helpful in this condition are (*a*) peritoneoscopy and (*b*) the humbler diagnostic abdominal tap. Udwadia (1978), in a series of 384 peritoneoscopies, found tubercular lesions in 29 cases. These 29 cases were patients with abdominal symptoms and signs in whom all the standard tests had proved unhelpful. Udwadia concludes in his paper that peritoneoscopy has a 'great deal to offer' in the diagnosis of abdominal tuberculosis when it presents as ascites of obscure origin, with recurrent and chronic abdominal pain, with a lump in the abdomen and with pyrexia and loss of weight.

In 2 patients with abdominal symptoms seen at this hospital we were able to demonstrate AFB in the fluid obtained on diagnostic abdominal tap. One patient, while under treatment for pulmonary tuberculosis, developed abdominal distension and ascites some 18 months later. AFB were demonstrated on the third tap, thus firmly confirming our tentative diagnosis of abdominal tuberculosis. Incidentally, the value of repeated examinations of a pathological fluid is demonstrated. The second patient had no frank ascites.

Regarding the difficulty in diagnosing abdominal tuberculosis even at laparotomy referred to by Shukla and Hughes, we feel that if the omentum is adherent to the lesion, this favours an inflammatory rather than a neoplastic lesion. In this connection one has to state that the behaviour of the omentum in various intra-abdominal conditions does not seem to have been studied in depth.

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UDWADIA T. E. (1978) *Ind. J. Surg.* **40**, 91.

Br. J. Surg. Vol. 66 (1979) 371-372

Book reviews

Surgery of the Pancreas: a Text and Atlas

Edited A. M. Cooperman. 280 × 215 mm. Pp. 257+xiv, with 273 illustrations. 1978. London: Kimpton. £35·70.

THIS is an interesting volume, the authors having set out to produce a text and atlas of pancreatic disease for the practising clinical surgeon and surgical resident. The text is commendably brief and the illustrations clear and concise. I especially liked the brief concluding sections of personal observations and preferences which accompany some chapters. Somewhat less satisfactory is the approach to diagnosis which, while outlining in a capable manner the modern diagnostic techniques available, fails to arrange them in an order of priority and give them an overall evaluation. There is little cross-reference between the various diagnostic techniques mentioned and missing from this section of the book is the argued personal approach so evident in the section on operative management. The relationship of particular diagnostic techniques to surgical approaches and to operability is not well covered and the advantages and disadvantages of intraoperative diagnostic techniques are not sufficiently underlined.

There is a full discussion of contentious issues, such as the value of intraoperative biopsy of the pancreas and the operative treatment of acute pancreatitis. The section on pseudocyst is well presented but perhaps reveals an under-appreciation of the value of information to be gained from preoperative ultrasonic examination. The coverage of chronic pancreatitis is adequate for the average surgeon but perhaps somewhat brief for the specialist in the field, the real difficulties such as the necessity for total pancreatectomy and the niceties of the operation of subtotal pancreatectomy being dealt with somewhat sketchily. By contrast, there is a large section on thoracic splanchnicectomy and sympathectomy for relief of pancreatic pain despite the apt comment that the procedure seldom gives long term relief.

The discussion on cancer of the pancreas and periampullary region is comprehensive. Adequate mention is made of the use of diagnostic tests and the advisability of two-stage operation in some situations where the bilirubin level is high and renal function compromised. There is perhaps less comment than one would like to see on the recent, more frequent use of total pancreatic resection for pancreatic cancer and recent advances in this area require fuller discussion. The operation of pancreaticoduodenectomy is described at length and well illustrated, but again there is little discussion of the dangers and postoperative complications which may result, and a somewhat tedious homage to the views of George Crile jun. in his advocacy of conservative measures.

This book can be recommended for the general surgeon who is faced with an operative problem in pancreatic surgery and is of interest to the specialists.

L. H. BLUMGART

Pathology of Peripheral Nerves

Arthur K. Asbury and Peter C. Johnson. 270 × 185 mm. Pp. 311+xii. Illustrated. 1978. Eastbourne: Holt–Saunders. £15·00.

THE main aim of this excellently produced and very readable book is to educate general pathologists in a field that is often a mystery to them, and because of this orientation it will be a valuable reference book for all who have occasional contact with peripheral nerves. The presentation of modern ideas about peripheral nerves and their disorders simply, concisely and fully makes this book a must for specialists also. Trauma, tumours, metabolic and diabetic neuropathies are general topics covered and there is a useful practical description of the technique of sural nerve biopsy. The quality of the photomicrographs is outstanding.

PAMELA M. LE QUESNE

A Practice of Anaesthesia

Edited H. C. Churchill-Davidson. 4th edition. 240 × 160 mm. Pp. 1542+xviii. Illustrated. 1978. London. Lloyd-Luke. £26·00.

THE fourth edition of this standard anaesthetic text will maintain its position on the reading list of every postgraduate student of the subject. This edition has lost one of its founder author/editors, Dr Wylie, but has increased the number of assistant editors who cover a wide range of special interests.

There are many changes. The assistant editors have completely rewritten some chapters and expanded others, though the book retains its form and clarity of layout. Many of the original illustrations and diagrams are included, which will give the book a 'familiar' appearance for those who have used it extensively for reference and examination preparation.

Chapters on paediatric anaesthesia, placental transfer and the development of anaesthetic apparatus are included in this volume for the first time. The chapter on paediatric anaesthesia enables the non-specialist postgraduate student to find the basic information assembled in logical order. Dr Reynolds's excellent chapter on placental transfer of respiratory gases and drugs provides a welcome addition to the text. The outline of the development of anaesthetic apparatus is most interesting to read, with illustrations of these historic pieces of equipment which many readers may never have had the opportunity to see.

Other changes include reference to the role of prostaglandins, a description of the more recent anaesthetic agents, the now commonly used circulatory support drugs and a less detailed but broader description of mechanical ventilation and ventilators. In keeping with current development, SI units are included, but unfortunately only in parentheses.

J. HULF

Guide to House Surgeons in the Surgical Unit

G. J. Fraenkel, J. Ludbrook and H. A. F. Dudley. Sixth edition. 150 × 120 mm. Pp. 203+xii. Illustrated. 1978. London. Heinemann. £2·90.

THIS is an excellent book filling a gap between university graduation and the fully qualified, registered state through which young doctors have to survive many pitfalls. The main theme of the book is to give the houseman a thorough understanding of his role in a modern teaching hospital, without at any time forgetting that the whole aim of the exercise is to provide diagnosis and treatment combined with consideration and kindness for the sick patient. Most housemen will know in theory what should be done, but in practice and in order of preference many investigations require programming. This exercise runs from the personal touch, following up request cards by telephone calls, fulfilling the role of guide, philosopher and friend to patients, and at times that of minor executive in regard to senior colleagues while at the same time listening to advice from all paramedical and non-medical personnel who, as this book says, 'by their very permanence have a knowledge and authority which can be most useful if properly exploited!' The influence of one of its authors can be seen particularly in the flow diagrams for dealing with patients who have, for example, retention of urine, undiagnosed liver disease and postoperative mental dysfunction; this latter flow chart, however, seems to have been photoreduced to fit the page and certainly reminded this reviewer that it is several years since he had the visual acuity of a houseman! Some change of typeset would encourage and help clarity in this figure. That apart, the book is to be warmly and wholeheartedly recommended to those embarking on a career as a houseman, for it is up-to-date, well indexed and full of good counsel from experienced authors. It also fits neatly into a white coat pocket.

J. B. ELDER

Frobisher and Fuerst's Microbiology in Health and Disease

Robert Fuerst. Fourteenth edition. 250 × 166 mm. Pp. 648+ix. Illustrated. 1978. Eastbourne: Holt–Saunders. £10·00.

Review of Medical Microbiology

E. Jawetz, J. L. Melnick and E. A. Adelberg. Thirteenth edition. 260 × 185 mm. Pp. 550+xiv. Illustrated. 1978. Los Altos, Ca. Lange. $12.00.

BOTH of these 1978 editions give a wide coverage of microbiology but one gains the impression that, of the two books, the microbiology review is the more up to date. Both apportion considerable space to bacterial physiology and genetics and rudimentary immunology, which, though of interest, are not directly relevant to surgical practice. However, despite the inevitable overlap of subject content they are in many ways complementary to one another rather than repetitive.

Frobisher and Fuerst's contribution is perhaps best described as being toward the 'ecology of microbiology'. Diseases and organisms are discussed from the standpoint of their environmental origin so that anthrax and gas gangrene, for example, are grouped together under 'bacterial pathogens of the soil'. Commensurate with this environmental approach, 'factors in transmission of communicable disease' and the role of 'microorganisms in our ecological system' are discussed. An entire section is also included in which the topics of sterilization, disinfection and a general consideration of antibiotics and chemotherapy are presented.

By contrast the *Review of Medical Microbiology* devotes more than half of its 41 chapters, concisely but without excessive detail, to a systematic description of bacteria, fungi, viruses and parasites which includes their pathogenesis, diagnosis and treatment. This method of approach lends itself more readily to the surgeon seeking information regarding a microbiological problem. There is also discussion of practical relevance regarding the use of the more commonly employed 'hospital' antibiotics and a chapter on the 'principles of diagnostic medical microbiology', which may well have been written more for the surgeon (or physician) than the microbiologist.

In conclusion, despite the readability and excellent illustrations of Frobisher and Fuerst's textbook, one feels that it would be to the *Review of Medical Microbiology* that the surgeon would turn in time of need.

MICHAEL J. SHIELD

Surgical Skills in Patient Care

Charles W. Van Way III and Charles A. Buerk. 265 × 185 mm. Pp. 173. Illustrated. 1978. St Louis: Mosby. £9·20.

THERE has been a tendency in recent years to disparage technical skill in medicine in favour of controlled trials and *P* values. On the other hand, mere technique must not be an end in itself. That is why the title of this book is so apt—it puts surgical skills in their right context. The procedures described are those used by all kinds of doctors in everyday patient care. The authors have been involved in teaching techniques such as asepsis, suturing, tying knots, local nerve blocks and wound care to junior doctors and students and the book is the result of that experience.

It is very readable, more so than some larger, older books on the subject. The diagrams are clear and appropriate and the ring binding means that the pages lie open while a particular procedure is being studied. This is particularly useful when following the instructions on tying knots! The sections are concise enough for the doctor to revise the technique before doing a liver biopsy, cut-down or tracheostomy.

One or two errors detract a little from the overall authority of the book: for example, if a chest drain is secured by a suture criss-crossing obliquely up the drain (p. 120), when the loops slip down and become transverse they will loosen and the drain will come out; the diagram of the subcuticular wound closure (p. 64) makes the suture look distinctly subcutaneous.

An extensive index adds to the overall usefulness and the book as a whole can be warmly recommended.

A. G. JOHNSON

Basic and Clinical Immunology

Edited H. H. Fudenberg, D. P. Stites, J. L. Caldwell and J. V. Wells. Second edition. 255 × 180 mm. Pp. 758. Illustrated. 1978. California. Lange. $14.50.

THIS very large book covers all aspects of immunology. Your reviewer has studied those chapters of surgical interest. As this is a multi-author book (with a dazzling cast), the comments may not reflect the whole picture.

The book is well laid out with clear diagrams. References appear at the end of each chapter; however, they are not cited in the text and they could be more comprehensive.

The chapter on transplantation immunology is brief and well written, with a good concluding overview; it has unfortunately been overhauled by recent developments in DR antigen matching. The same author contributes a longer chapter on the histocompatibility complex, but at the expense of this, the surgeon would surely prefer a fuller account of transplantation immunology; nowhere is there a detailed account of the events in acute rejection. Similarly a chapter on immune cell traffic might have been included. The chapter on tumour immunology is a model of good writing and is to be recommended to anyone with even a passing interest in the subject. Cellular and non-cellular mediators of the immune response are well described as are the tests of cellular function.

Overall, a well-written book, with the emphasis on clarity. The book is not comprehensive enough for a reference book yet it is too large for the primary fellowship; however, at the price it is an exccellent buy for anyone beginning to take a serious interest in immunology.

R. W. BLAMEY

Nervous Tunnel Syndromes of the Limbs from Non-traumatic Etiology

N. Marchetti, P. Bachechi, E. Barbieri and G. Guido. 245 × 180 mm. Pp. 188. Illustrated. 1978. Padova: Liviana Editrice. No price given.

MOST orthopaedic surgeons have dealt with several varieties of 'tunnel syndromes' and have read of many more. Those specializing in the surgery of peripheral nerves will have had a wider experience, but few can have seen the encyclopaedic collection described by the authors of this book. All the recognized non-traumatic varieties of peripheral nerve compression are described. The text is in Italian and there is a parallel English version: the text is well illustrated.

The style is dogmatic and the English translation quaint. I was particularly interested in the section on writer's cramp, said by the authors to be due to compression of the median nerve in the forearm, but different from the pronator teres syndrome. Physical and electromyographic signs were absent but decompression of the nerve relieved the symptoms.

This book should find a place on the shelves of libraries and of those surgeons interested in the surgery of peripheral nerves; it will be a useful reference book. I would not recommend it for undergraduates or for trainee surgeons, since it may give them the false impression that there is nothing more to be added to the subject.

M. WATSON

Gynaecological Laparoscopy

The report of the working party of the confidential inquiry into gynaecological laparoscopy. 210 × 150 mm. Pp. 165. Illustrated. 1978. London: Royal College of Obstetricians and Gynaecologists.

THIS important volume has been well reviewed in a number of places and deservedly so. It represents a formidable amount of work but more important, as with the confidential obstetric inquiries, an honest analytical approach which surgeons in other fields could do well to emulate. Some form of audit (a word used fearlessly in the introduction) is coming upon us. The techniques and attitudes described here are a model for self-protective audit, which we should adopt, lest it is done for us, and possibly against us, by others.

H A. F. DUDLEY

SURGICAL PROBLEMS IN THE AGED

Edited by K. D. J. VOWLES, MB, CHB, FRCS
Consultant Surgeon, Devon and Exeter Clinical Area

with a Foreword by
SIR FERGUSON ANDERSON, OBE, MD, FRCP, FRFPS, KStJ

Contents: Foreword; Surgery for the aged; Assessment before surgery; Anaesthesia for the aged; The problem of dysphagia; Gastroduodenal problems; Biliary tract and pancreatic problems; Problems with hernia, the small intestine and the appendix; Colonic and rectal problems; Urological problems; Problems of the aged hip; Vascular problems and the aged amputee; Postoperative problems in the aged; Index.

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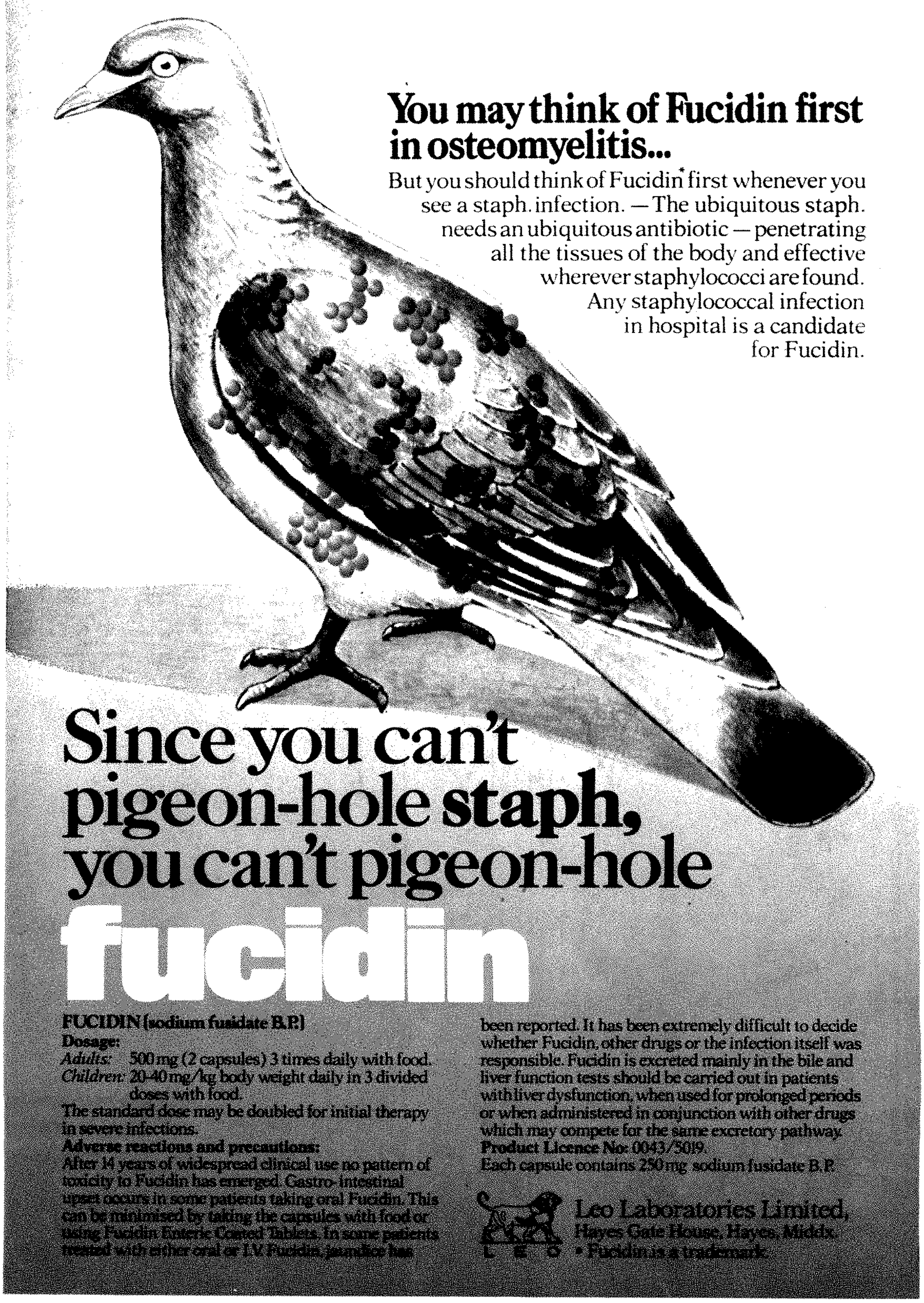

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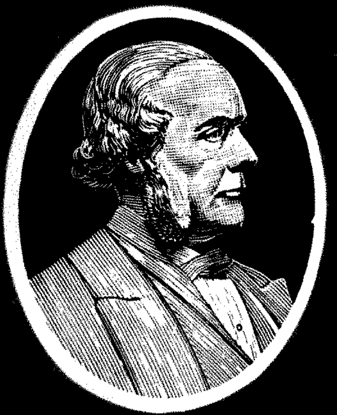

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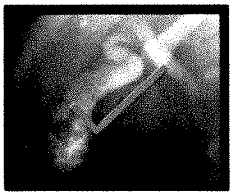
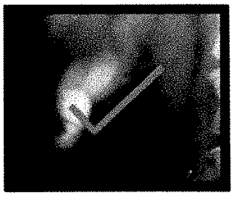
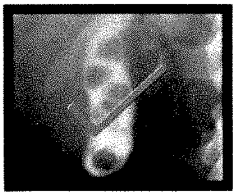
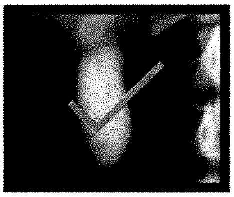
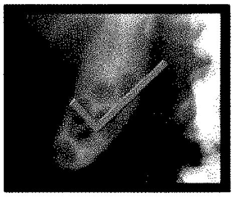
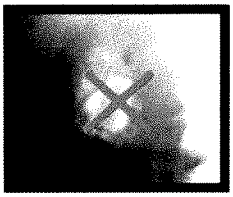

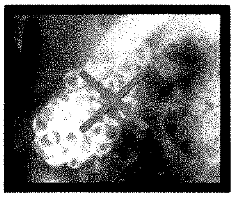
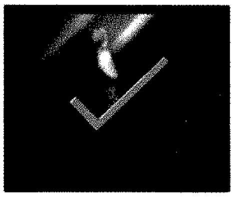

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Reference 1. Maton, P. N., Iser, J. H., Murphy, G. M. and Dowling, R. H. (1977) Efficacy of withdrawal from and resistance to chenodeoxycholic acid treatment in patients with gallstones. Gut, *18*, A976 (abstract).

2. Thistle, J. L., Hofmann, A. F., Ott, B. J. and Yu, P. Y. S. (1976) Gallstone dissolution with chenodeoxycholic acid 1969 - 1976. The Mayo Clinic Studies. Gastroenterology, 70, 943 (abstract).

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The *British Journal of Surgery* subscribes to the policy of uniform requirements for manuscripts described in *British Medical Journal* 1979; **1**: 532–5 and *Lancet* 1979; **1**: 428–31, which authors are advised to consult, and in the leaflet *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, which is available from the Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR (enclose 50p). The recommendations below are those which contributors to this journal *must* observe.

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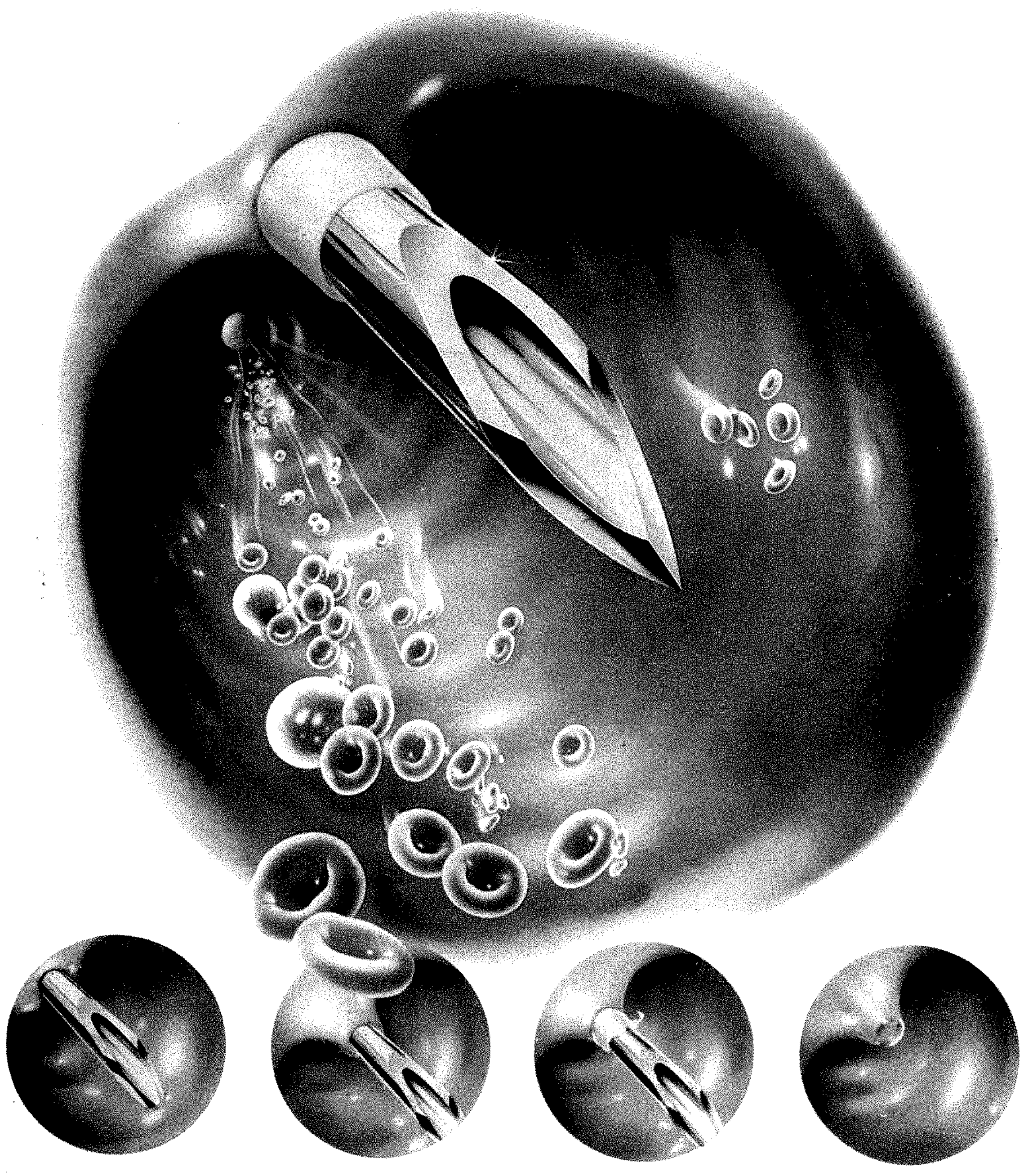

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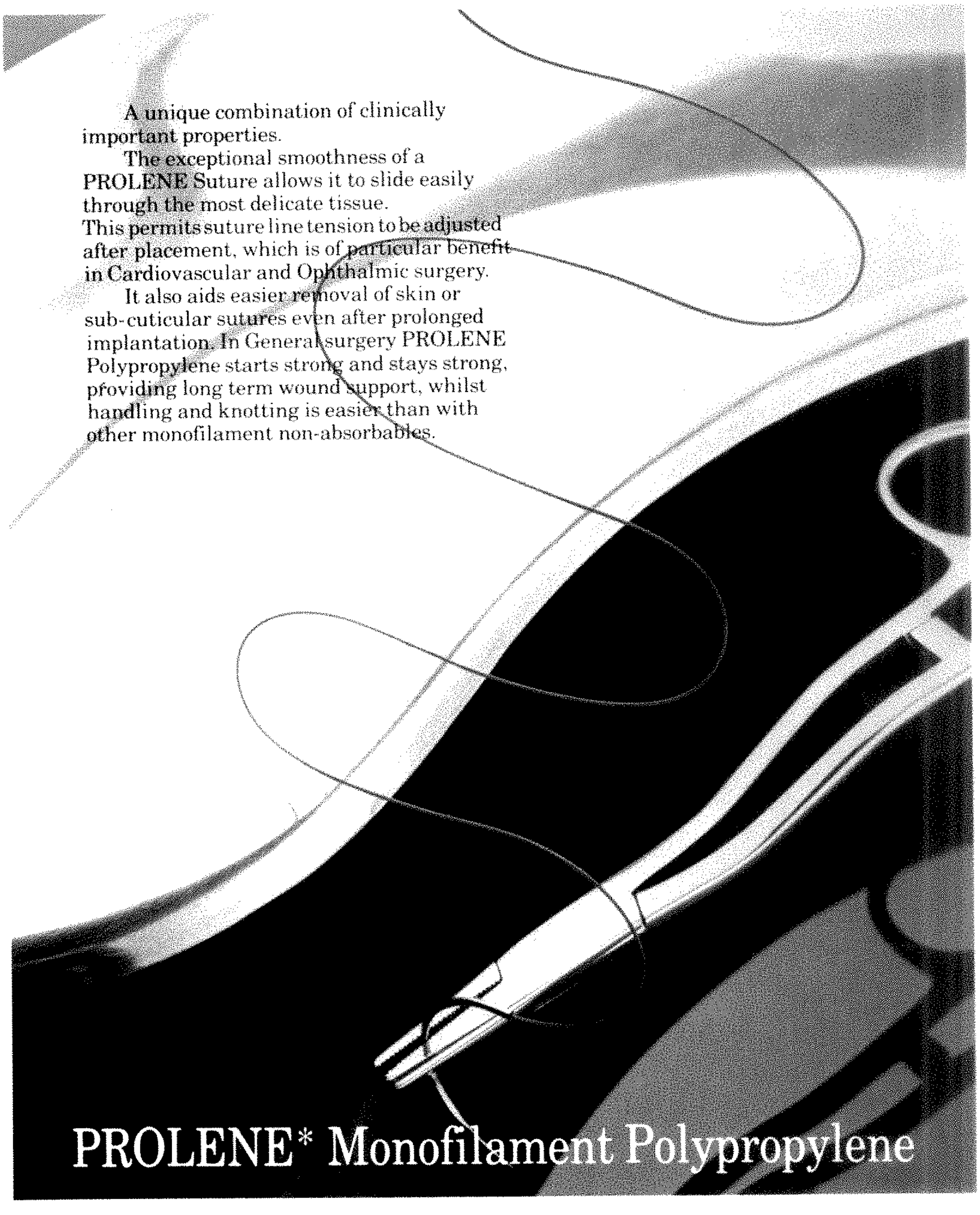

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1. J. int. med. Res. (1977) 5 (Suppl. 3): 86-91.
2. ibid., 101-108. **3.** ibid., 98-100.
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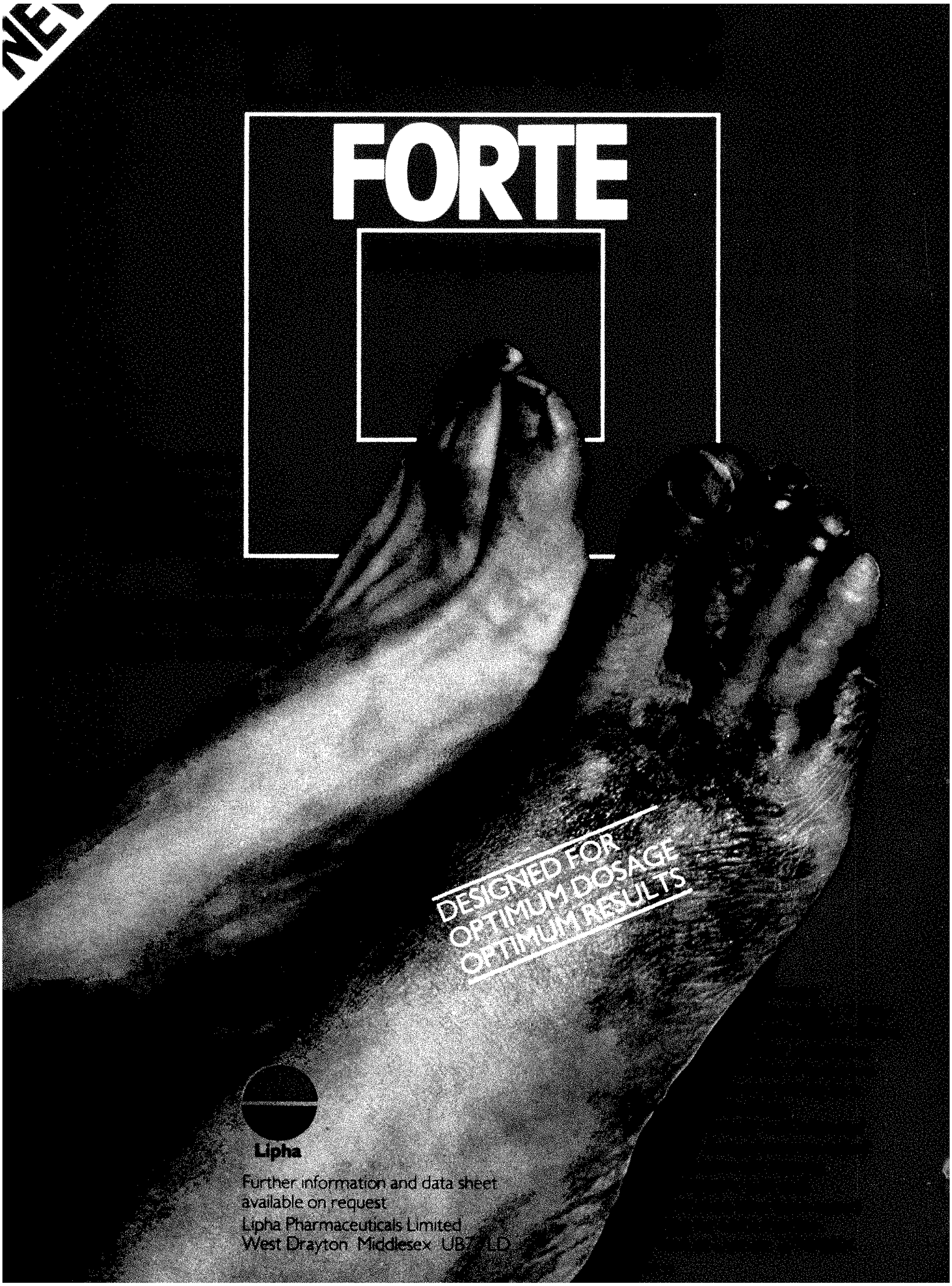

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Br. J. Surg. Vol. 66 (1979) 373–378

The management of insulin tumours of the pancreas

L. P. LE QUESNE, J. D. N. NABARRO, A. KURTZ AND S. ZWEIG*

SUMMARY

A series of 26 patients diagnosed as having an insulin-secreting, islet-cell tumour of the pancreas is described. Three patients were treated medically, but in the remaining 23 the tumour was found at operation; 1 patient had a carcinoma with hepatic metastases, but in the other 22 the tumour was apparently benign and the subsequent course of these patients has confirmed this conclusion.

The tumour was found at the initial operation in 19 of the 22 patients with a benign tumour treated surgically. Of the other 3, the tumour was removed at a second operation in 2 and at a third operation in 1. Two of the 22 patients died following the operation.

Diazoxide was administered to 21 patients, before and/or after operation. It was given preoperatively to 17 patients, in all of whom it prevented the development of hypoglycaemic symptoms, but in 2 it caused serious fluid retention and had to be discontinued. Seven patients have been successfully treated with long term diazoxide, either as an alternative to surgery or following an unsuccessful operation, 1 of these being the patient with an islet-cell carcinoma. In these patients diazoxide has been given for up to 12 years without apparent side effects.

Selective coeliac angiography was performed in 13 patients. In no patient did it provide critical information that significantly influenced the treatment of the patient.

Percutaneous, transhepatic portal venous catheterization was performed in 4 patients and indicated the site of the tumour in 3, 2 of whom had had 1 previous operation and 1 had had 2 previous operations, at none of which was a tumour found: in all 3 patients the tumour was removed at a subsequent operation.

The application of these findings to the management of patients with an insulinoma is discussed and a scheme of management is proposed.

BETWEEN 1962 and 1978, 26 patients with an insulin-secreting tumour of the pancreas have been treated at The Middlesex Hospital. Our experience in the management of these patients is reported, with particular emphasis on the results of preoperative angiography in the localization of these tumours, and on the use of diazoxide in the control of hypoglycaemia. The management of patients with this condition is discussed in the light of this experience.

Patients and methods

The present series comprised 16 women and 10 men, their ages ranging from 18 to 70 years (*Table 1*). A benign tumour was removed from 22 patients: 1 patient (*Case* 2) had a carcinoma with metastases and the condition ultimately proved fatal. The 3 remaining patients were treated medically and their tumours are presumably benign.

All the patients presented with neurological symptoms, usually attacks of confusion, loss of consciousness or fits. Three patients, following typical, transient attacks occurring intermittently over several months, developed prolonged coma. Two of these (*Cases* 14 and 16) were admitted in a state of decerebrate rigidity; following maintenance of normoglycaemia with diazoxide a tumour was removed and both have made remarkable recoveries, although they have some permanent impairment of cerebral function.

Diagnosis

The diagnosis of hypoglycaemia was based on finding a low blood sugar ($<2\cdot2$ mmol/l) either after an overnight fast (18 patients) or during prolonged fasting (5 patients). In the other 3 patients the diagnosis was based on the history and on an abnormal blood sugar to serum insulin relationship. The fact that the hypoglycaemia was due to excess insulin was demonstrated by finding a disproportionately high serum insulin for the blood sugar either after overnight or prolonged fasting (*Fig.* 1).

In the first patient in the series the fact that the hypoglycaemia was of islet-cell origin was demonstrated by an intravenous tolbutamide test, but thereafter this test was not used as a diagnostic procedure.

Diazoxide

Diazoxide was given to 17 patients before operation. The initial dose was 50 mg 8-hourly. In all patients control of the blood sugar level and symptoms was successfully obtained, but to achieve this the dose had to be increased to 450 mg daily in several patients, and 1 patient (*Case* 14) required 1·2 g daily before control was achieved. In 2 patients the drug caused serious fluid retention, leading in one patient (*Case* 23, 150 mg daily) to left ventricular failure and in the other (*Case* 17, 450 mg daily) to a pericardial effusion. Both conditions resolved promptly on withdrawal of the drug.

In 3 patients (*Cases* 6, 18 and 22) no tumour was found at the initial operation and these patients were subsequently maintained symptom-free on diazoxide; details of these patients are given below. An operation has not been performed on 3 older patients (*Cases* 8, 12 and 25); their symptoms have been controlled on diazoxide, one of them having been on treatment with 150 mg/day for 7 years. Diazoxide was also

---

* The Middlesex Hospital, London.

Table I: DETAILS OF PATIENTS WITH AN INSULINOMA

Case no.	Age (yr)	Sex	Site of tumour	Angiography	Diazoxide	Treatment
1	57	F	Neck	—	—	Distal pancreatectomy
2	55	F	Head (malignant)	—	Yes	Partial hepatectomy
3	18	M	Head	—	—	Enucleated
4	43	M	Tail	—	—	Enucleated
5	58	F	Tail	—	—	Distal pancreatectomy
6	40	M	Uncinate process	Yes	Yes	1. Blind distal pancreatectomy 2. Exploration 3. Enucleation (died)
7	40	F	Neck	—	—	Distal pancreatectomy
8	55	F	—	—	Yes	Medical
9	35	F	Tail		Yes	Enucleated
10	37	M	Head	—	Yes	Enucleated
11	63	F	Body	Yes	Yes	Enucleated
12	70	F	—	—	Yes	Medical
13	50	F	Tail	Yes	Yes	Enucleated
14	34	F	Head	Yes	Yes	Enucleated
15	35	F	Head	Yes	Yes	Enucleated
16	32	F	Tail	Yes	Yes	Distal pancreatectomy
17	33	M	Head	Yes	Yes	Enucleated
18	60	M	Body	Yes	Yes	1. Exploration 2. Distal pancreatectomy
19	26	M	Head	Yes	Yes	Enucleated
20	21	F	Head	Yes	Yes	Enucleated (died)
21	47	F	Neck	Yes	Yes	Enucleated
22	51	F	Tail	Yes	Yes	1. Exploration 2. Distal pancreatectomy
23	32	F	Body	Yes	Yes	Distal pancreatectomy
24	30	M	Tail	—	Yes	Distal pancreatectomy
25	74	M	—	—	Yes	Medical
26	21	M	Uncinate process	—	Yes	Enucleated

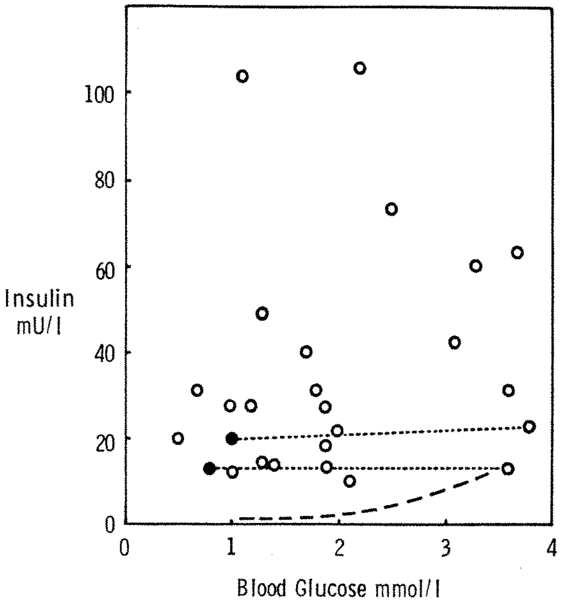

Fig. 1. Simultaneous fasting blood sugar and serum insulin levels in 24 patients with an insulinoma. The dashed line (– – –) represents the upper limit of serum insulin in 12 normal subjects rendered hypoglycaemic with fish insulin (Turner and Harris, 1974). The open circles (○) denote the levels obtained after an overnight fast. In 2 patients the overnight fast did not produce a diagnostic result and the test was repeated after a prolonged fast (●); in both patients this repeat test confirmed the diagnosis.

given to the patient with an islet-cell carcinoma with liver metastases; the attacks were controlled with this drug until the patient's death 10 months later.

Coeliac angiography

Coeliac angiography was performed preoperatively in 13 patients, subtraction films being made in 10. To assess the contribution of this examination to the management of each patient, the surgeon was not informed of the result of the angiogram before operation, and the films were consulted only when a tumour had been located or when the surgeon was satisfied that he could not find it.

In 10 of these 13 patients the tumour was found without undue difficulty. In 6 the tumour had been correctly located by the arteriogram. In 3 of the remaining 4 no tumour had been demonstrated on arteriography, and in the fourth patient the angiogram was reported as showing a tumour in the head of the pancreas whereas at operation a tumour was found in the tail; the patient was cured by resection of the tumour.

In 3 patients no tumour could be felt at operation. In 2 patients (*Cases* 6 and 18, *see below*) no tumour was demonstrated radiologically. In the third patient (*Case* 22, *see below*) the angiogram suggested, but did not definitely show, the presence of a tumour in the head of the pancreas, but even after repeated palpation it could not be indentified. The abdomen was closed without resection of any pancreatic tissue and at a subsequent operation a tumour was identified in the tail of the pancreas. The results of the angiographic examination are summarized in *Table II*.

The angiograms of 6 patients resulted in correct localization of the tumour. Five were in the head of the pancreas (maximum diameter 0·5–1·5 cm) and 1 in the body (diameter 2·0 cm). In 7 patients the tumour was not visible on the angiogram. Of these, 3 were in the tail (maximum diameter 0·8–1·5 cm), 2 in the body (0·8 and 1·5 cm diameter), 1 in the neck (0·8 cm diameter) and 1 in the uncinate process (1·2 cm diameter).

Operative treatment

In 23 patients the pancreas was explored through a transverse supraumbilical incision. In 19 a benign tumour was found at the initial operation, simple enucleation being performed in 13. In the remaining 6 patients, in whom the tumour was in the tail, a limited distal pancreatectomy, together with splenectomy, was performed. One of the patients having enucleation of the tumour from the head of the pancreas died postoperatively (*Case* 20); she developed a peripancreatic abscess requiring drainage, followed by prolonged ileus and a pancreatic fistula; death followed an episode of profuse vomiting with aspiration. The remaining 18 patients were cured by the removal of the tumour.

The management of the 3 patients in whom no tumour could be found at the original operation is described in detail, as is that of one patient (*Case* 23) who presented unusual diagnostic difficulties.

Case 6: Blind distal pancreatectomy was performed at the initial operation but no tumour was found in the resected specimen. The patient was adequately controlled on diazoxide for 2 years, when a further laparotomy was performed. No tumour was demonstrated on preoperative angiography and none was found at operation. Following this operation the patient remained symptom-free on diazoxide for 12 years, after which he again developed hypoglycaemic attacks, despite increasing doses of the drug. The results of a percutaneous transhepatic portal vein catheterization were difficult to interpret, but suggested the presence of a tumour at the junction of the head of the pancreas with the uncinate process. An ultrasound examination also indicated the presence of a tumour in the same area. At the third operation exposure of the pancreas was difficult owing to the presence of dense, very vascular adhesions. Eventually a soft tumour, almost impalpable in the surrounding gland, was detected in the uncinate process, posterior to the superior mesenteric vessels, and further severe haemorrhage occurred during its removal. Operation was followed by numerous complications and the patient eventually died, 63 days postoperatively, as the result of sepsis in the portal area. (The initial stages of this patient's history have been recorded previously by Mengoli and Le Quesne, 1967.)

Case 18: No tissue was excised at the first operation, and postoperatively the patient was treated with diazoxide. After 2 years he was requiring increasing doses of this drug but arteriography failed to reveal a tumour. Transhepatic catheterization of the splenic vein was performed by Dr R. Dick at the Royal Free Hospital, samples of blood being withdrawn at measured distances from the splenic hilum. The insulin content of these samples was measured and the results suggested the presence of an adenoma in the body of the pancreas. Following this a further laparotomy was performed but again no tumour could be palpated. A distal pancreatectomy was performed, the line of pancreatic division being judged from its relation to the lumbar spine to lie to the right of the indicated position of the tumour. Serial slicing of the removed portion of the pancreas revealed a 8-mm diameter adenoma 1 cm from the line of section. This patient has remained symptom-free since operation. (Details of the catheterization study in this patient have been reported by Turner et al., 1978.)

Case 22: Despite an arteriogram suggesting, but not definitely indicating, a tumour in the head of the pancreas, no tumour could be felt at operation. As a preoperative trial of diazoxide had shown that it would control the patient's symptoms, the abdomen was closed without resection of any pancreatic tissue. The patient remained symptom-free on diazoxide 150 mg daily, but was readmitted for reassessment 12 months later owing to a weight gain of 12 kg. Percutaneous transhepatic catheterization of the splenic vein (*Fig.* 2) indicated the presence of a tumour in the tail of the pancreas. At a second operation a 12-mm tumour was found in the tail of the pancreas, 4–5 cm from the tip. Distal pancreatectomy and splenectomy was performed and the patient made an uneventful recovery. The patient was mildly diabetic for 3 days after operation, excluding the presence of a second tumour in the head of the pancreas.

Case 23. This 31-year-old lady had had infrequent episodes of confusion for 5 years before referral to The Middlesex Hospital in 1977. On prolonged fasting the blood sugar fell to 1·3 mmol/l and the patient became confused. A number of overnight fasting blood sugar and insulin level measurements were made with the results shown in *Table III*. The first three pairs of blood sugar and serum insulin levels would lie above the dotted line in *Fig.* 1 while the last three fall below it. (The figures for January 1977 are shown in *Fig.* 1.) It seemed possible that this patient had an insulinoma that was only partially autonomous. Arteriography did not reveal a tumour. Diazoxide therapy led to pulmonary oedema and had to be discontinued. Two days after stopping the diazoxide transhepatic splenic vein catheterization was performed by Dr Dick, but the serum insulin levels were all low and there was no indication of the site of the adenoma. An untrasound scan suggested that there might be an adenoma in the neck of the pancreas.

At operation a dumb-bell-shaped tumour (maximum dimension 1·5 cm) was found in the distal part of the body of the pancreas; it was removed by distal pancreatectomy. Histological examination showed a benign islet-cell adenoma and the patient has remained free from attacks in the 18 months since operation.

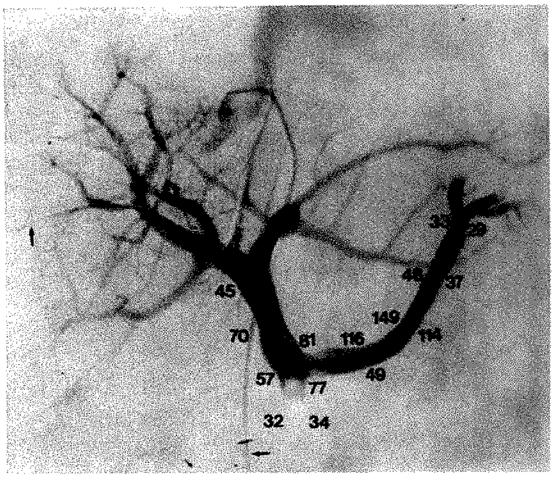

Fig. 2. Results of the percutaneous transhepatic catheterization study in *Case* 22. The concentration of insulin (mU/l) at measured intervals along the splenic superior mesenteric and portal veins is superimposed on a phlebogram. The catheter was passed twice along each of the former two veins, and the results of the two studies are shown on either side of each vein. The abrupt increase in concentration of insulin in the middle sample from the splenic vein clearly indicates the site of the tumour. In this patient, in addition to the catheter inserted into the portal system (↑), a catheter was also passed into a hepatic vein (←).

Table II: CORRELATION OF ANGIOGRAPHY WITH OPERATIVE FINDINGS

	Tumour shown	Tumour not shown
Tumour felt	6	4
Tumour not felt	0	3

Table III: BLOOD SUGAR AND SERUM LEVELS IN CASE 23

	1975		Jan. 1977	Feb. 1977		
Fasting blood sugar (mmol/l)	2·5	2·3	1·9	2·0	2·2	3·0
Fasting serum insulin (mU/l)	8	9	13	2·2	2·5	3·7

Discussion

The establishment of a firm diagnosis that a patient's symptoms are due to organic hyperinsulinism, the commonest cause in an adult being a solitary, benign adenoma of the B-cells of the islets of Langerhans, involves two steps: (*a*) the demonstration that the symptoms are caused by hypoglycaemia and (*b*) that this is accompanied by excess, inappropriate insulin secretion.

Once the possibility of the diagnosis has been considered it is usually a straightforward procedure to establish that the attacks are due to hypoglycaemia, a diagnosis firmly linked in surgical writings with the features of Whipple's triad. In the majority of patients the development of hypoglycaemia (blood sugar <2·2 mmol/l) can be provoked by an overnight fast, but as with 5 of our patients, a fast of up to 48 h may be required. With the development of sensitive methods of measuring serum insulin by immunoassay techniques it is now possible to provide direct evidence that the hypoglycaemia is due to hyperinsulinism, by demonstrating a disproportion between the fasting blood sugar and serum insulin levels (Turner et al., 1971, 1973; Turner and Harris, 1974). In a normal person, if the blood sugar falls to a low level, serum insulin becomes almost undetectable, but in a patient with an insulinoma, insulin secretion is no longer suppressed by this 'feedback' mechanism. It is usually possible to demonstrate this imbalance between sugar and insulin levels by measuring levels of both in an overnight fasting blood sample. Even if a clear imbalance is shown, it is wise to repeat the examination at least once, as its implications are so important. If hypoglycaemia is not provoked by this method, it may be necessary to prolong the fast for up to 48 h, as shown by two of the subjects in *Fig.* 1. If this is unsuccessful, hypoglycaemia can be produced by injection of a fish insulin that does not cross-react in the assay with human insulin, so that it is possible to detect whether endogenous insulin secretion has been suppressed by the hypoglycaemia (Turner and Harris, 1974). A further possibility is to produce hypoglycaemia by the injection of ordinary commercial insulin and monitor endogenous insulin production by measuring the level of C-peptide. This peptide is the connecting link between A and B chains of insulin and is released when any insulin is being secreted by the patient's pancreas.

Despite the wide recognition of the features of hypoglycaemia, the diagnosis of an insulinoma can be difficult. In a review of 60 patients with an insulinoma seen at the Mayo Clinic, Service et al. (1976) found that the time from the initial attack to the establishment of the diagnosis ranged from 10 days to 15 years, the average being 32·5 months. The importance of an early diagnosis is underlined by *Cases* 13 and 24 in the current series, both of whom suffered long periods of unconsciousness before the diagnosis was suspected and confirmed, and both of whom have some residual permanent impairment of cerebral function. It should be emphasized, however, that even if there has been severe cerebral damage, the tumour should be removed if possible, as a remarkable degree of recovery may occur.

The results of this study show clearly that diazoxide is very effective in preventing hypoglycaemic episodes in patients with an insulinoma. There were no failures of treatment in the 21 patients in this series to whom it was administered: 7 patients were successfully maintained on this drug for periods of up to 12 years with no untoward late complications. In the early stages of administration of the drug, however, its effects must be observed carefully, both to adjust the dosage correctly and to check that it is not causing excessive fluid retention, a complication which necessitated withdrawal of the drug in 2 of our patients. This fluid retention is secondary to sodium retention, probably caused by increased sodium and water reabsorption in the proximal tubules as a consequence of the vasodilatory action of the drug (Pohl et al., 1972). The long term administration of diazoxide is a valuable alternative to removal of the tumour in those few patients in whom an operation is, for any reason, contraindicated. In addition to this clear-cut indication for its use, we believe that the patient's response to diazoxide should be assessed before operation in all cases, unless the site of the tumour has been clearly demonstrated before operation (*see below*).

In most patients with an insulinoma the definitive treatment is to perform an operation to identify and remove the tumour. Usually the tumour can be identified without great difficulty, but in some patients it may be impossible to locate it at operation. With this in mind, it is usually recommended that coeliac axis arteriography should be performed before operation in an attempt to demonstrate the tumour. Using a special technique involving selective injection of the individual arteries of the pancreas, Clouse and his colleagues (1977) demonstrated 8 of 10 tumours, but by the use of the conventional techniques of injection into superior mesenteric and coeliac vessels the success rate is only some 40–45 per cent (Harrison et al., 1973; Robins et al., 1973; Fulton et al., 1975), and is influenced by the size of the tumour. In assessing the significance of these results it must be borne in mind that the great majority of tumours can be detected at operation, and the crucial question to be answered is whether angiography can locate those tumours, usually small, which the surgeon is unable to palpate. It was with this consideration in mind that the study reported here was undertaken. In the event, in 3 patients the surgeon was unable to detect a tumour at operation, and in none did the angiogram give information enabling the tumour to be removed. Angiography was performed in a further 10 patients, in all of whom the tumour was detected at operation without undue difficulty. In 6 of these the tumour was correctly located by angiography, in 3 no tumour was shown and in the last patient the angiogram suggested a tumour in the head of the pancreas whereas at operation it was found to be in the tail.

We believe that this study casts serious doubt on the value of coeliac axis angiography in the localization of insulinomas. It is true that in about half the patients it will give clear guidance to the surgeon as to where he can expect to find the tumour, but even then the remainder of the pancreas will require careful examination to exclude a second tumour. Our study provides no evidence that the examination provides critical information about the site of the tumour in those patients in which it is most needed. Harrison et al. (1973) state that in 2 patients the arteriogram located a tumour that they could not palpate, but beyond this we can find no evidence from the literature that this is a frequent occurrence. In our opinion, the value of the information to be gained from conventional coeliac axis angiography does not justify the discomfort to the patient.

If no tumour can be found at operation the conventional surgical treatment is to perform a blind distal pancreatectomy. In a previous paper (Mengoli

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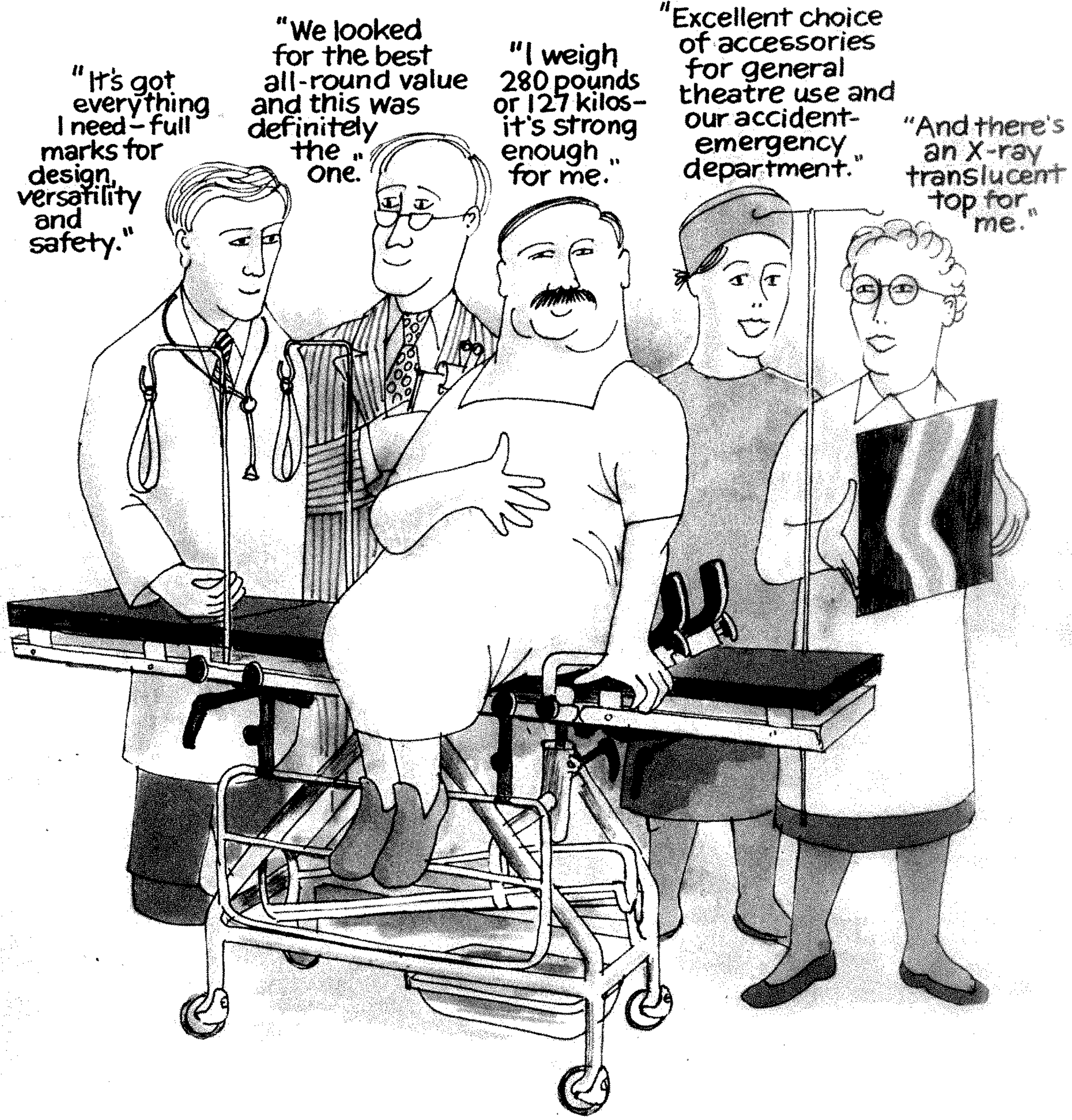
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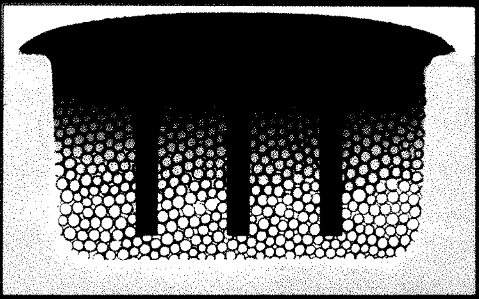

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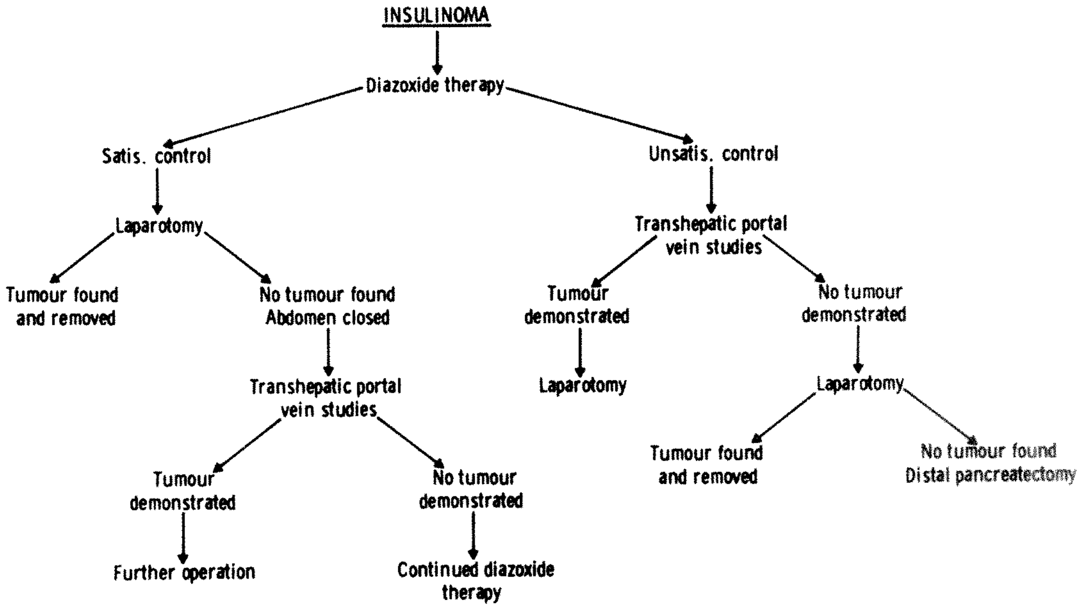

Fig. 3. Scheme for the management of patients with an insulinoma.

and Le Quesne, 1967) we drew attention to the fact that this procedure failed to remove the tumour in three-quarters of the patients on whom it was performed. In the light of this finding we suggested that, if the patient's hypoglycaemia could be controlled by diazoxide, this operation should not be performed, but the abdomen closed and the tumour sought for again at a second operation a year or more later by which time the tumour might have increased in size sufficiently to make its presence apparent.

This idea that, with the passage of time, the tumour will increase in size significantly would appear to be wrong. In a review of 542 cases of insulinoma, Stefanini et al. (1974) could find no evidence of a relationship between length of history and size of the tumour. Furthermore, in only 35 per cent of 168 patients undergoing a second operation for an occult tumour was the tumour identified at a subsequent operation, the remaining 65 per cent of the patients requiring a further blind resection to remove the tumour. Stefanini and his colleagues recommend that, if a tumour cannot be found at the initial operation, the correct procedure is to perform 'a progressive excision of the head of the pancreas from left to right guided by immediate pathological examination of the removed specimen, and by continuous measurement of the blood sugar concentration'. Bearing in mind that the studies of both Mengoli and Le Quesne (1967) and Stefanini et al. (1974) show that the majority of occult tumours are in the head of the pancreas, the implementation of this policy must result, in many of these patients, in the removal of a major portion of the pancreas, with its unavoidable consequences of both exocrine and endocrine insufficiency. Furthermore, it is by no means clear that continuous estimation of the blood sugar concentration can be relied upon to indicate that the tumour has been removed (Harrison et al., 1973).

The development of the new techniques of tumour localization by percutaneous transhepatic catheterization of the portal vein and possibly by ultrasound may well make obsolete this crude operation of blind distal resection of pancreatic tissue. The localization of an insulin tumour by percutaneous transhepatic catheterization of the splenic and portal veins was first described by Ingemansson et al. in 1975, and in 1977 Ingemansson et al. reported the localization of islet-cell hyperplasia in the tail of the pancreas by this technique. In 1978 Turner et al. reported 2 further patients in whom the tumour was successfully located before operation by this technique (one of these patients being *Case* 18 from this series). In addition, they described a modification of this technique in which the splenic vein is catheterized at operation and the blood samples analysed by a special rapid technique which gives the results of insulin assay in 50 min. Using this technique, which depends upon the same principle as the percutaneous preoperative examination, they successfully located 7 of 8 tumours. In the current series, a preoperative examination was carried out in 3 patients in addition to *Case* 18 (previously reported by Turner et al., 1978), and the tumour was located in 2. In the patient in whom the examination failed, there was evidence suggesting that the tumour only secreted intermittently. This evidence suggests that this technique is the most accurate available method for the localization of an insulinoma. In addition, our experience with 2 patients suggests that ultrasound may be a valuable technique for localizing these tumours.

Clearly, further experience is required before the exact place of catheterization of the portal venous system in the management of patients with an insulinoma can be defined. Such experience may in fact show that transhepatic catheterization should be performed in all patients before operation, but there is to date insufficient evidence to justify this conclusion. Furthermore, it is unlikely that the peroperative technique, which depends upon a very specialized technique of insulin assay, will ever be widely applicable. We believe, however, that the evidence at present available, together with the accumulated experience with the use of diazoxide, clearly indicates that, provided it is known that the patient's symptoms can be controlled safely with this drug, no patient should be submitted to blind distal resection without a prior portal vein catheter study. A scheme of management, based on the preoperative administration of diazoxide and designed to reduce to the minimum the need to perform a blind resection, is set out in *Fig*. 3. A similar scheme, based on the use of arteriography before operation and portal vein studies on the operating table, has been proposed by Turner et al. (1978).

Acknowledgements

It is a pleasure to acknowledge our gratitude to our colleagues in the Department of Radiology who carried out the arteriographic studies, and we are particularly indebted to Dr M. Raphael, who performed two of the percutaneous transhepatic splenic vein catheter studies.

References

CLOUSE M. E., COSTELLO P., LEGG M. A. et al. (1977) Subselective angiography in localizing insulinomas of the pancreas. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **128**, 741–746.

FULTON R. E., SHEEDY P. F., MCILRATH D. C. et al. (1975) Preoperative angiographic localization of insulin-producing tumour of pancreas. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **123**, 367–377.

HARRISON T. S., CHILD C. G., FRY W. J. et al. (1973) Current surgical management of functioning islet-cell tumours of the pancreas. *Ann. Surg.* **178**, 485–493.

INGEMANSSON S., KUHL C., LARSON L. et al. (1977) Islet-cell hyperplasia localized by pancreatic vein catheterization and insulin radioimmunoassay. *Am. J. Surg.* **133**, 643–645.

INGEMANSSON S., LUNDERQUIST A., LUNDQUIST I. et al. (1975) Portal and pancreatic vein catheterization with radioimmunologic determination of insulin. *Surg. Gynecol. Obstet.* **141**, 705–711.

MENGOLI L. and LE QUESNE L. P. (1967) Blind pancreatic resection for suspected insulinoma: a review of the problem. *Br. J. Surg.* **54**, 749–756.

POHL J. E. F., THURSTON H. and SWALES J. D. (1972) The antidiuretic action of diazoxide. *Clin. Sci.* **42**, 145–152.

ROBINS J. M., BOOKSTEIN J. J., OBERMAN H. A. et al. (1973) Selective angiography in localizing islet-cell tumours of the pancreas. *Radiology* **106**, 525–528.

SERVICE F. J., DALE A. J. D., ELVEBACK L. R. et al. (1976) Insulinoma: clinical and diagnostic features of 60 consecutive cases. *Mayo Clin. Proc.* **51**, 417–429.

STEFANINI P., CARBONI M., PATRASSI N. et al. (1974) The surgical treatment of occult insulinomas: a review of the problem. *Br. J. Surg.* **61**, 1–4.

TURNER R. C. and HARRIS E. (1974) Diagnosis of insulinomas by suppression tests. *Lancet* **2**, 188–190.

TURNER R. C., LEE E. C. G., MORRIS P. J. et al. (1978) Localization of insulinomas. *Lancet* **1**, 515–518.

TURNER R. C., OAKLEY N. W. and NABARRO J. D. N. (1971) Control of basal insulin secretion, with special reference to the diagnosis of insulinomas. *Br. Med. J.* **1**, 132–135.

TURNER R. C., OAKLEY N. W. and NABARRO J. D. N. (1973) Changes in plasma insulin during ethanol-induced hypoglycaemia. *Metabolism* **22**, 111–121.

Paper accepted 15 December 1978.

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A new look at the arterial supply of the bile duct in man and its surgical implications

J. M. A. NORTHOVER AND JOHN TERBLANCHE*

SUMMARY

The blood supply of the human bile duct has been re-evaluated using high resolution resin casts prepared from 24 fresh human cadavers. The refined technique used yielded casts of all vessels, including capillaries, and produced a clear picture of the blood supply of the human bile duct for the first time. The arterial supply of the supraduodenal duct was shown to be axial, with the main vessels, which have been named the 3 o'clock and 9 o'clock arteries, running along the lateral borders. The retroportal artery, which has not been described by previous workers, was present in all complete casts and was a major source of the axial blood supply to the supraduodenal duct in 32 per cent of them.

The major importance of this new knowledge of bile duct blood supply may well lie in the understanding of the aetiology of postoperative bile duct strictures and in their prevention. An explanation is proposed for the long strictures sometimes seen after minimal surgical trauma to the bile duct, based on damage to the small vessels supplying the duct; guidelines to prevent such damage are presented. Ischaemia of the bile duct may also explain some of the biliary problems that have followed human liver transplantation and other procedures involving biliary anastomosis, such as Whipple's operation.

THE arterial supply of the bile duct is a neglected subject, despite the large amount of biliary surgery being performed today. Textbooks of surgery and anatomy give it little attention, while the few publications on the subject differ widely in their conclusions.

The precise pathogenesis of postoperative bile duct strictures is as yet not fully explained. The generally held view is that operative trauma to the ducts is the main cause, but the mechanism whereby reputedly minimal surgical trauma can lead to almost total disappearance of the extrahepatic bile ducts in some patients remains a matter for speculation. Major interference with bile duct blood supply may be an important factor (Appleby, 1959).

Biliary complications remain a major stumbling block to progress in human liver transplantation (Calne, 1977). It has been suggested that poor blood supply to the donor bile duct may be responsible (Calne, 1972). The present anatomical study was initiated to investigate this problem. The potential importance of bile duct blood supply in the pathogenesis of bile duct strictures only became evident during the course of the study.

Materials and methods

Anatomical specimens were collected from 24 human cadavers within 12 h of death: all were previously fit adults who had died of non-abdominal trauma. A resin casting technique was used based on that of Tompsett (1970) but extended to allow casting of all vessels down to capillary size (Northover et al., 1979).

After maceration of the tissue in acid, dissection of the resin casts themselves was carried out. Extensive photography and, in some cases, scanning electron microscopy were employed to record the blood supply of the bile duct in each cast.

Results

The cast

Because total vascular replication, including the capillary bed, was achieved using this technique, the perfused organs were replaced by microvascular casts closely resembling the original organs (*Fig.* 1*a*). Thus, for instance, the duodenal cast could be opened to reveal that the mucosal villi were faithfully represented by resin casts of their capillaries. The same degree of resolution was achieved with the bile duct, where the mucosal capillary cast was well demonstrated by scanning electron microscopy (*Fig.* 2).

Major vessel anatomy

Although most textbooks describe a pattern of major arteries as shown in *Fig.* 3, this precise configuration was seen in only 2 (8 per cent) of the specimens in this series. This accords with the experience of previous workers, who have noted great anatomical variability in this region (Flint, 1923; Daseler et al., 1947).

Arteries supplying the duct

Twenty-one casts were of sufficient quality to allow definitive evaluation of the arterial supply of the bile duct. To facilitate description of its blood supply the duct has been subdivided into three segments, namely hilar (right and left hepatic ducts), supraduodenal (common hepatic duct and upper common bile duct) and retropancreatic (lower common bile duct). The supply of the supraduodenal duct will be described in detail as it is surgically the most important segment.

Supraduodenal duct: The supply of this segment was essentially axial, i.e. most vessels to the supraduodenal

Table I: MAJOR ARTERIES SUPPLYING BRANCHES TO THE SUPRADUODENAL BILE DUCT IN 21 CASTS

Artery	Casts in which the bile duct received arteries from this source	
	Total	%
Retroduodenal artery and main branches	17	81·0
Right hepatic artery	16	76·2
Cystic artery	11	52·4
Gastroduodenal artery and main branches*	9	42·9
Retroportal artery (arising from coeliac axis)	9	42·9
Retroportal artery (arising from superior mesenteric artery)	9	42·9
Left hepatic artery	5	23.8
Common hepatic artery	3	14.3
Others	5	23·8

* Excluding its most important branch, the retroduodenal artery.

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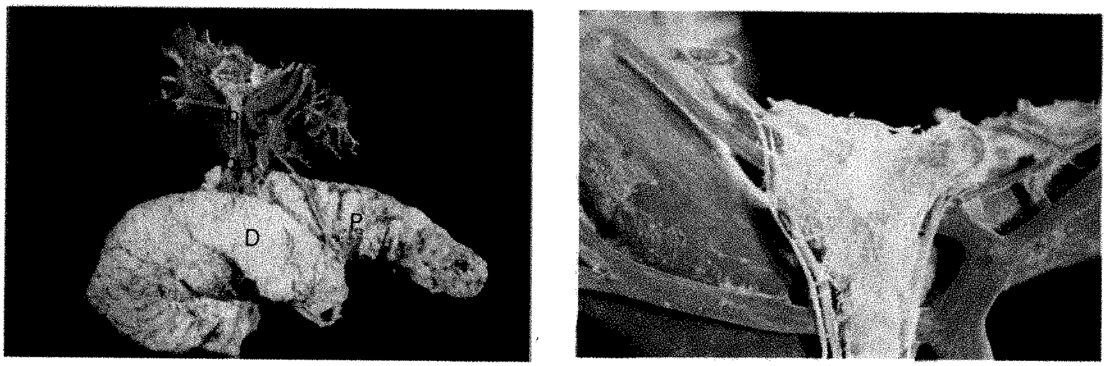

Fig. 1. *a*, A resin cast at an early stage of dissection. Note that there is no tissue present in this specimen. Casts of the gallbladder, cystic duct, central portion of the supraduodenal duct and most of the liver have been removed. The 3 o'clock and 9 o'clock arteries and veins (arrowed) are seen at the lateral borders of the supraduodenal duct (b). *b*, Close-up view of the upper common hepatic duct cast to show precise relations of the 3 o'clock and 9 o'clock vessels (the veins appear mauve due to slight transcapillary passage of red resin). A series of small arteries and veins leaves these axial vessels to form the plexus around the duct. In this specimen the 3 o'clock and 9 o'clock vessels extend to a higher level than usual. (P, pancreas; D, duodenum.)

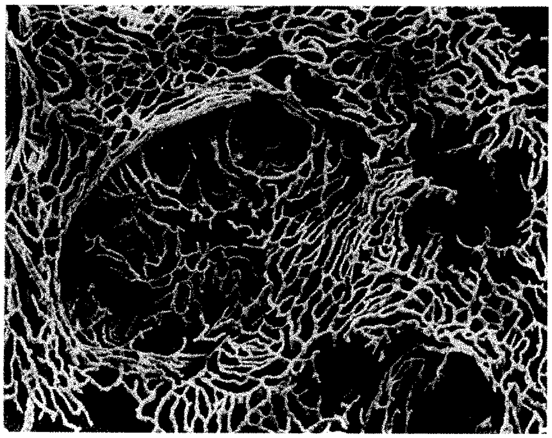

Fig. 2. A scanning electron micrograph of a resin cast of the bile duct mucosal capillaries. A 1-mm oval pit, at left centre, lined by capillaries, is typical of those seen in the mucosa of the bile duct. (×40.)

duct arose from named arteries related to its upper and lower ends (*Table I*). On average, 8 small arteries, each about 0·3 mm in diameter, supplied the supraduodenal duct. The most important of these axial vessels ran along the lateral borders of the duct; as these vessels have not been adequately described or named previously we have called them the 3 o'clock and 9 o'clock arteries (*Figs.* 1, 3, 4). One or both of these arteries was present in all specimens. Many of the other vessels supplying the duct arose from the retroduodenal and gastroduodenal arteries below (*Fig.* 5). On average, 60 per cent of vessels reaching the supraduodenal duct ran upwards from the major vessels below; 38 per cent of vessels ran downwards from the right hepatic and other arteries, while only 2 per cent of the supply was non-axial arising from the trunk of the common hepatic artery (*Fig.* 6, *Table II*).

An important source of supply to the supraduodenal duct was a vessel not described by previous workers, which has been named the retroportal artery (Northover and Terblanche, 1978). This vessel, which was present in all the casts, arose posteriorly from either the coeliac axis or superior mesenteric artery close to their origin from the aorta (*Table III*). From its origin it passed to the right, behind the portal vein and on to the back of the head of the pancreas to reach the lower end of the supraduodenal duct (*Figs.* 7, 8). From this point the further course of the artery varied. In about half the casts the artery terminated by joining the retroduodenal artery close to the lower end of the supraduodenal duct (*Fig.* 7); in these specimens small branches from the trunk of the retroportal artery passed on to the posterior surface of the duct—this has been designated the type I pattern. In a third of the casts the type II pattern

Table II: RELATIVE PROPORTIONS OF TOTAL ARTERIAL SUPPLY OF THE SUPRADUODENAL BILE DUCT FROM VARIOUS SOURCES, EXPRESSED AS PERCENTAGES OF TOTAL SUPPLY (DERIVED FROM SUMMATED DATA IN 21 CASTS)

Direction of supply	Artery of origin	% of total arterial supply	
From below	Retroduodenal artery	26.9	60·1
	Retroportal artery	15·8	
	Gastroduodenal artery	9·9	
	Others	7·5	
From above	Right hepatic artery	25·5	38·0
	Cystic artery	7·5	
	Left hepatic artery	3·1	
	Others	1·9	
From left	Common hepatic artery	1·9	1·9

Table III: ORIGIN OF RETROPORTAL ARTERY IN 20 CASTS

Artery of origin	No. of casts
Coeliac axis and major branches	9
Superior mesenteric artery and major branches	9
Joint origin from coeliac axis and superior mesenteric artery	1
Retroportal artery replaced by aberrant right hepatic artery arising from superior mesenteric artery	1

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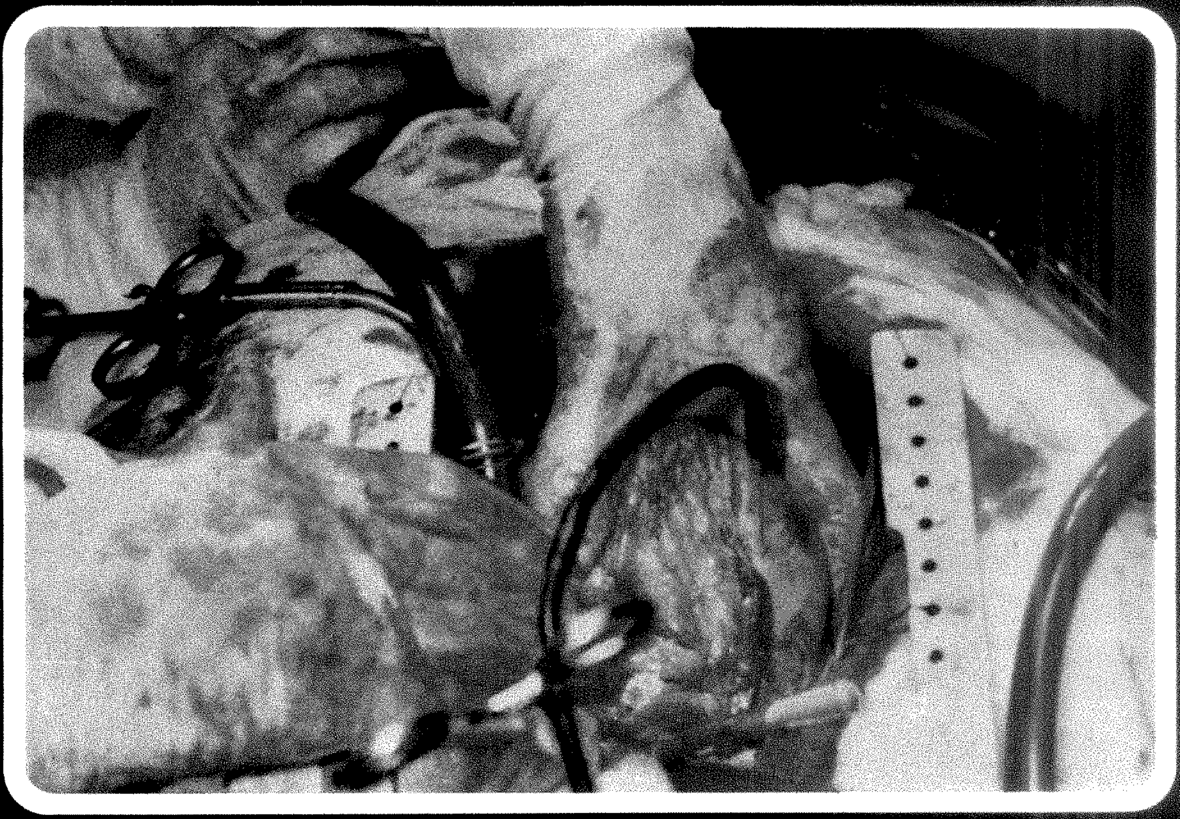

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1 Brit med J (1978), **1**, 1603
2 Thorax (1978), 33, **1**, 130
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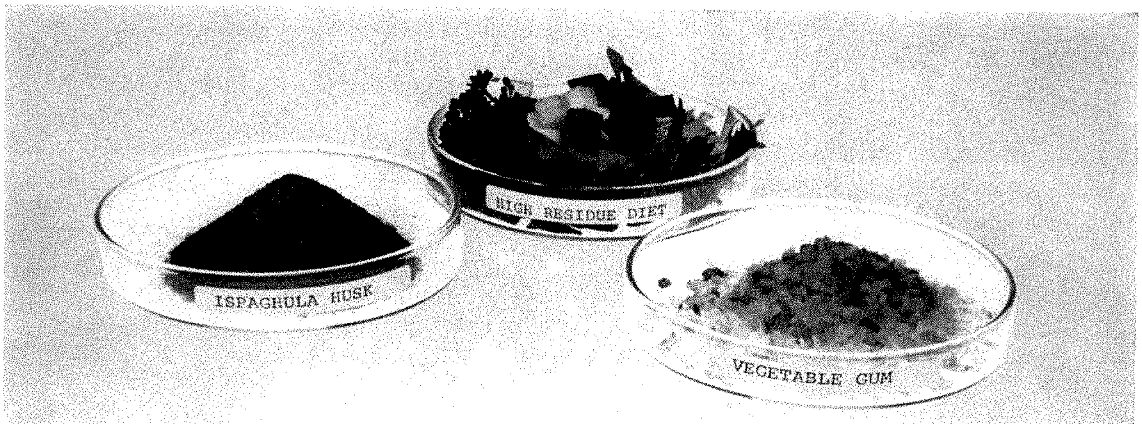

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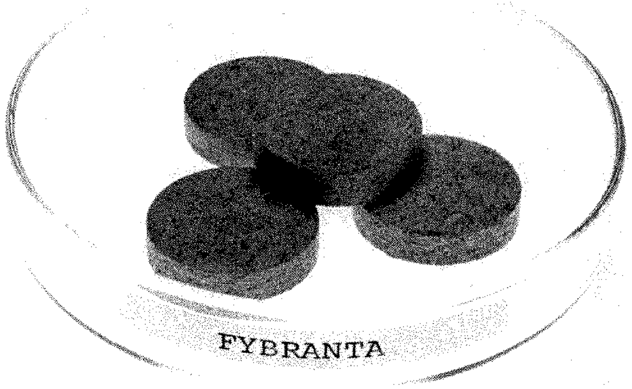

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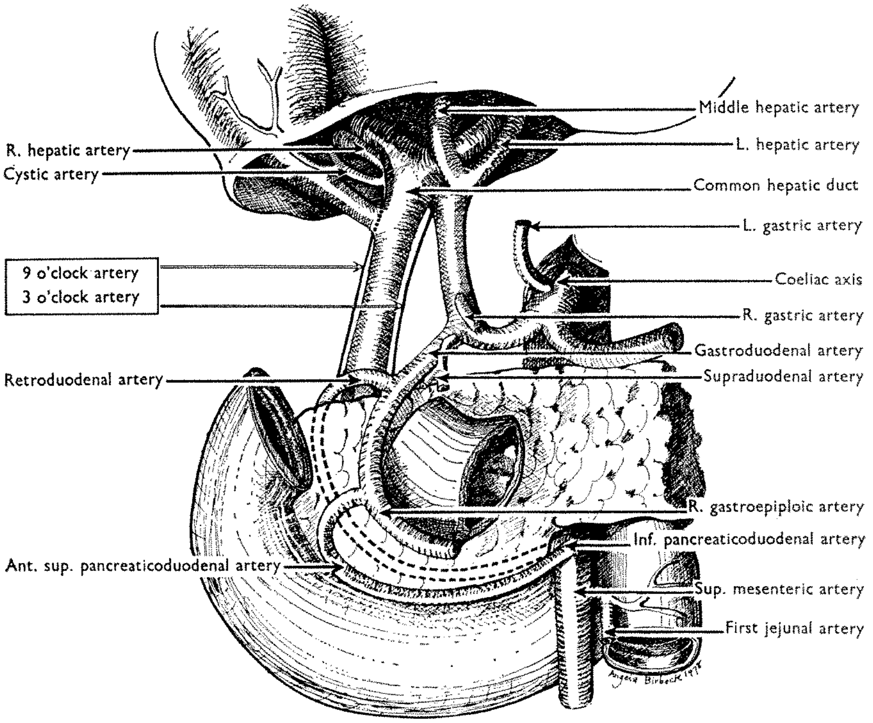

Fig. 3. The major arteries related to the supraduodenal bile duct. Part of the duodenum has been omitted to reveal the origin of the retroduodenal artery from the gastroduodenal artery.

prevailed (*Fig.* 8), in which the retroportal artery itself passed upwards on the back of the supraduodenal duct and joined the right hepatic artery behind the common hepatic duct. *En route* it gave branches which joined the pericholedochal plexus. Unlike the type I retroportal artery, which supplied the supraduodenal duct solely from below, the type II retroportal artery played a major role in supplying the duct from above by virtue of its truncal connection with the right hepatic artery.

Hilar ducts: These ducts were usually closely related to the left and right hepatic arteries and received a copious supply of small arteries from these trunks, forming a rich network on the surface of the ducts, in continuity with the plexus around the supraduodenal duct. In some casts the 3 o'clock and 9 o'clock arteries extended upwards to contribute to the supply of the hilar ducts (*Fig.* 1).

Retropancreatic duct: The pattern of supply of this segment resembled that of the hilar ducts in that the duct was closely related to a parallel major artery, i.e. the retroduodenal artery, which provided multiple small vessels running around the duct to form a mural plexus (*Fig.* 9).

Intramural arteries of the bile duct

The axial arteries of the supraduodenal duct (3 o'clock, 9 o'clock and type II retroportal arteries) and the many small vessels surrounding the hilar and retropancreatic ducts gave rise to multiple arteriolar branches which formed a free anastomosis within the wall of the bile duct. No end-arteries were noted in this series. The arteriolar plexus in turn gave rise to the capillary plexus. Using the scanning electron microscope, the mucosal capillary plexus was clearly demonstrated to be made up of vessels 10–16 μm in diameter (*Fig.* 2).

Discussion

A clear understanding of the blood supply of the human bile duct, which has hitherto not been available, may provide important clues to the pathogenesis of bile duct strictures and may explain the high incidence of biliary leakage and sludge formation when direct bile duct anastomosis is employed in human liver transplantation (McMaster et al., 1978).

The eight papers on the arterial supply of the bile duct which have appeared in the world literature of the past 30 years differ fundamentally in their conclusions (Douglass and Cutter, 1948; Shapiro and Robillard, 1948; Henley, 1955; Munkácsi and Siklós, 1960; Michels, 1962; Parke et al., 1963; Ranga and Andronescu, 1966; Pförringer, 1971). These differences have major surgical implications. On the one hand, Shapiro and Robillard (1948) suggest that the duct is supplied by a few end-arteries, damage to any of which would surely lead to stricture and anastomotic leakage, while at the other extreme Douglass and Cutter (1948) found an abundant plexus around the duct, so that nothing short of skeletonization would critically damage the blood supply. Such disparate conclusions must raise doubts about the reliability of the techniques used in some of these studies. The technique employed in the present study proved highly satisfactory. The use of fresh cadavers minimized small vessel loss by autolysis, while the casting technique produced organ replicas which lent themselves easily to microdissection and scanning electron microscopy.

While previous studies have tried simply to determine which major arteries supply small vessels

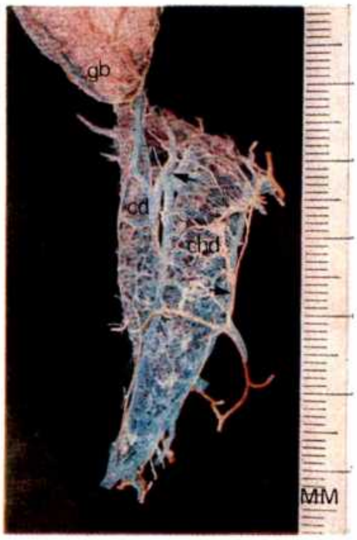

Fig. 4. An isolated cast of the supraduodenal and cystic ducts. The 3 o'clock and 9 o'clock arteries and veins (arrowed) are seen at the borders of the supraduodenal duct; attempts to flush-tie the cystic duct (cd) could damage the 9 o'clock vessels. Small arteries are seen joining the main axial vessels from above and below. Note the millimetre scale on the right. (gb, gall bladder; chd, common hepatic duct.)

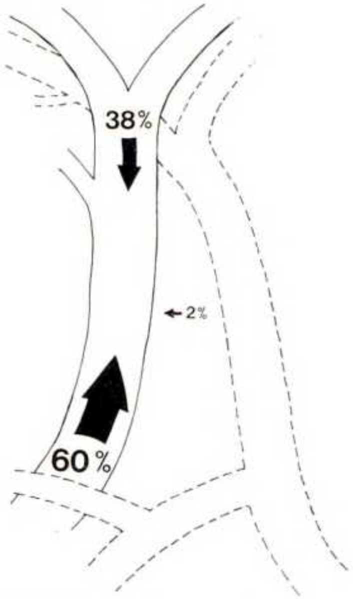

Fig. 6. Mean percentage (to the nearest whole number) of supraduodenal bile duct arterial supply from various directions. Note that the vast majority of vessels reach the duct in axial fashion.

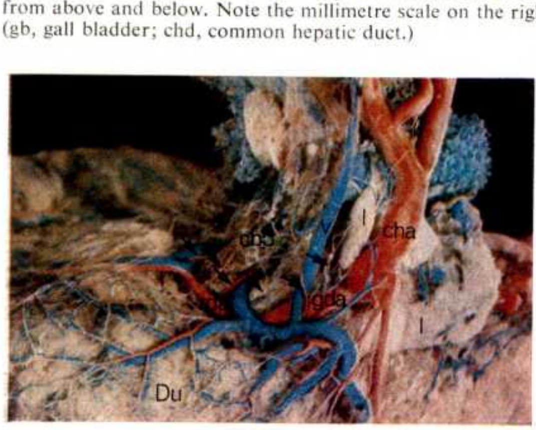

Fig. 5. Anterior view of structures in the free edge of the lesser omentum: the common bile duct (cbd) and common hepatic artery (cha) lie in front of the portal vein which is almost hidden from view. The first part of the duodenum (Du) is seen below, with the gastroduodenal artery (gda) and its retroduodenal branch (rda) lying behind it. These two arteries give six axial arteries (arrowed) to the supraduodenal duct. A very large 3 o'clock vein (v) is present. Lymph node capillary casts (l) surround the common hepatic artery.

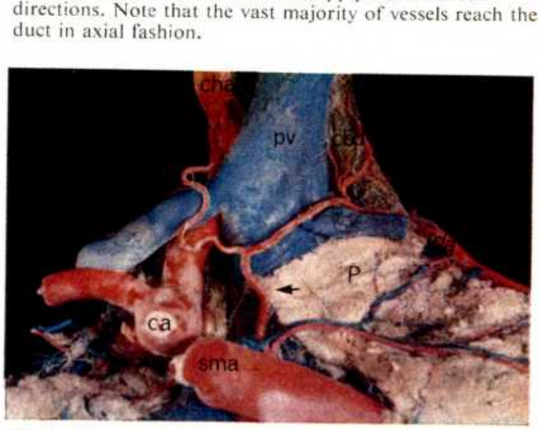

Fig. 7. Posterior view of a cast to show a type I retroportal artery. The origins of the coeliac axis (ca) and superior mesenteric artery (sma) can be seen below the splenic vein. The retroportal artery (arrowed) arises from the superior mesenteric artery and crosses the back of the portal vein (pv); in this cast it gives off a branch which joins the common hepatic artery (cha). The retroportal artery passes between the portal vein and the supraduodenal bile duct (cbd) to join the retroduodenal artery (rda) although the junction is hidden from view by the duct. As it passes the duct it gives off several branches which join the periductal plexus. Note that the duodenal cast has been removed. (P, head of the pancreas.)

to the duct, the present study has also attempted to quantify the supply from these various sources. It has shown that the axial supply to the supraduodenal duct is mainly from below; the retroduodenal artery, a vessel adequately described as late as 1941 (Edwards, 1941), provides the bulk of supply from this direction. The right hepatic artery contributes most of the supply from above.

The 3 o'clock and 9 o'clock arteries have not been fully described before, although they are almost always present, and readily damaged during surgical dissection. The 9 o'clock artery, at the right border of the duct, conforms with the marginal anastomotic loop noted by Douglass and Cutter (1948) and Parke et al. (1963).

The retroportal artery is another important vessel, though it has not been noted previously, perhaps because of its posterior position. Douglass and Cutter (1948) described one specimen in which an artery arose from the coeliac axis and passed through the substance of the pancreas to supply the distal common duct. This may well have been the first report of the retroportal artery, although it was not recognized as

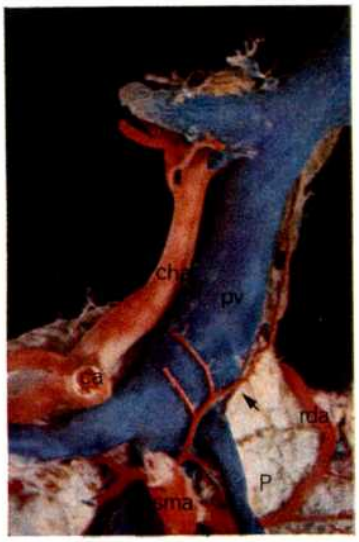

Fig. 8. Posterior view of a cast to show a type II retroportal artery. The coeliac axis (ca) and superior mesenteric artery (sma) are seen above and below the splenic vein. The retroportal artery (arrowed) arises from the superior mesenteric artery and passes across the back of the portal vein (pv) to reach the posterior surface of the supraduodenal bile duct (parts of which have been removed). The artery ascends to join the right hepatic artery, hidden by the right branch of the portal vein. Note that the duodenal cast has been removed. (P, head of the pancreas.)

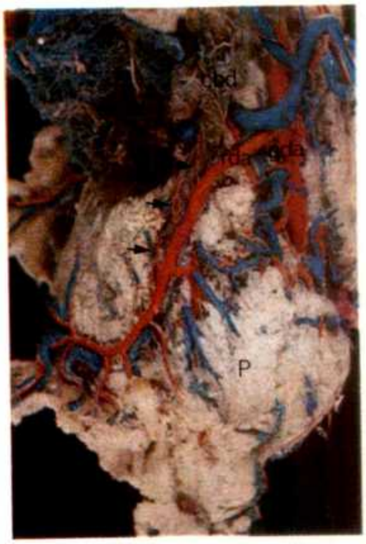

Fig. 9. To show the supply of the retropancreatic duct by the retroduodenal artery. The convex right lateral surface of the head of the pancreas (P), with the duodenum removed, is seen in the centre. The retroduodenal artery (rda) arises from the gastroduodenal artery (gda) in front of the pancreas and passes to the posterior surface of the latter to come into close contact with the retropancreatic bile duct (cbd), which it supplies with several arteries (arrowed).

such at the time. The present study has shown this vessel to be constant in occurrence, though varying in its precise origin, its mode of termination and its contribution to the axial supply of the supraduodenal duct.

Bile duct strictures have been variously attributed to the necrotizing effect of bile, to ischaemia or to a combination of these factors. In 1950, Douglass et al. demonstrated that the marked fibrotic reaction occurring at a healing bile duct anastomosis in the dog was avoided if the anastomosis was protected by proximal bile diversion. Later Rains (1959) confirmed the propensity for bile to induce fibrosis. Cameron and Hou (1962), however, felt that ischaemia alone was the cause of duct stricture—they were able to induce this lesion by cross-clamping the bile duct of the guinea-pig for 1 min, thus inducing temporary segmental ischaemia. Appleby (1959) linked the two factors by suggesting that bile destroyed only ischaemic tissue, leaving normal tissue undamaged. Carlson et al. (1977) have recently shed light on the action of bile on duct tissue. In a study in which they ligated the bile duct in dogs, they showed that bile gained access to mural collagen via mucosal defects which appeared proximal to the site of the ligature. Bile then caused a disturbance in the cohesive forces in the collagenous matrix of the duct wall, leading to rapid collagen turnover and, ultimately, thickening of the duct wall.

Based on the anatomical data revealed in the present study and the findings of the workers mentioned above, we suggest that postoperative bile duct strictures may arise in the following manner. Ischaemia, whether caused directly by accidental duct clamping or indirectly by trauma to the bile duct blood supply, might damage ductal mucosa sufficiently to render it permeable to bile, which would then act on ischaemic tissue within the wall to induce inflammation and fibrosis. Oedema accompanying such a reaction might even occlude adjacent parts of the choledochal arterial plexus, as these vessels are only 0·3 mm or less in diameter. This would produce further ischaemia and lead to a spreading cycle of collagen breakdown and fibrosis until a large part of the duct has been destroyed. The supraduodenal duct is the area most likely to be damaged by this process, as its blood supply is more vulnerable than that of the hilar and retropancreatic segments.

The clearer understanding of the blood supply of the bile duct which has emerged as a result of this study has made it possible to define guidelines which should help to avoid damage to the blood supply of the supraduodenal duct during routine biliary surgery and hence, perhaps, to prevent some strictures. Dissection around the common bile duct should be restricted to that which is absolutely necessary for the particular procedure being undertaken; it should be especially avoided at the edges of the duct to preserve the 3 o'clock and 9 o'clock arteries and their branches to the choledochal plexus. Where possible, the cystic duct should not be divided flush with the common bile duct to avoid damage to the 9 o'clock vessels, and the cystic artery should be divided near the gallbladder to preserve its branches to the common duct. Dissection in the groove between the supraduodenal bile duct and the first part of the duodenum endangers the retroduodenal artery and its copious branches to the duct at this point. Finally, in performing Kocher's manoeuvre, the thin fibrous layer on the back of the head of the pancreas and portal vein should be left intact to preserve the retroportal artery.

Another important area in which a better understanding of bile duct blood supply should be of assistance is the field of biliary anastomosis. The implications in the bile duct reconstruction used in liver transplantation have been discussed elsewhere (Northover and Terblanche, 1978). The unacceptably high incidence of anastomotic complications that follows direct anastomosis of donor to recipient common bile duct in man (Williams et al., 1973; Starzl et al., 1976) stands in stark comparison with the uniformly good results obtained using the same anastomosis for liver transplantation in the pig and baboon; this difference may well be related to species differences in bile duct blood supply (Northover and Terblanche, 1978). In addition, it would appear that human liver transplant specimens with a type II retroportal artery have a better vascularized donor duct than those with the type I retroportal artery. McMaster has recently shown that the biliary sludge which so often complicates human liver transplantation, and which is usually found adhering exclusively to the wall of the donor duct, consists mainly of necrotic collagen (McMaster et al., 1978). This might well suggest that the operative procedure as it stands produces an ischaemic donor bile duct, which is likely to lead to healing problems. It has been suggested that most of the donor duct be sacrified, necessitating division at high donor common hepatic duct level, in order to provide a better perfused ductal remnant for successful anastomosis (Northover and Terblanche, 1978).

Biliary anastomotic leakage and stricture have been reported to be quite common after pancreaticoduodenectomy (Mongé et al., 1964; Gilsdorf and Spanos, 1973). This may be another situation in which compromise of the bile duct blood supply has led to serious postoperative complications which may be avoidable in the light of a better knowledge of the blood supply to the bile duct.

Acknowledgements

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References

APPLEBY L. H. (1959) Indwelling common duct tubes. *J. Int. Coll. Surg.* **31**, 631–643.

CALNE R. Y. (1972) Observations on experimental and clinical liver transplantation. *Trans. Proc.* **4**, 773–779.

CALNE R. Y. (1977) The present status of liver transplantation. *Trans. Proc.* **9**, 209–216.

CAMERON G. R. and HOU C. T. (1962) An experimental study of stricture of the common bile duct in the guinea-pig. *J. Pathol. Bacteriol.* **83**, 265–274.

CARLSON E., ZUKOSKI C. F., CAMPBELL J. et al. (1977) Morphological, biophysical and biochemical consequences of ligation of the common bile duct in the dog. *Am. J. Pathol.* **86**, 301–312.

DASELER E. H., ANSON B. J., HAMBLEY W. C. et al. (1947) Cystic artery and constituents of the hepatic pedicle: study of 500 specimens. *Surg. Gynecol. Obstet.* **85**, 47–63.

DOUGLASS T. C. and CUTTER W. W. (1948) Arterial blood supply of the common bile duct. *Arch. Surg.* **57**, 599–612.

DOUGLASS T. C., LOUNSBURY B. F., CUTTER W. W. et al. (1950) An experimental study of healing of the common bile duct. *Surg. Gynecol. Obstet.* **91**, 301–305.

EDWARDS L. F. (1941) The retroduodenal artery. *Anat. Rec.* **81**, 351–355.

FLINT E. R. (1923) Abnormalities of the right hepatic, cystic and gastroduodenal arteries, and of the bile ducts. *Br. J. Surg.* **10**, 509–519.

GILSDORF R. B. and SPANOS P. (1973) Factors influencing morbidity and mortality in pancreaticoduodenectomy. *Ann. Surg.* **177**, 332–337.

HENLEY F. A. (1955) The blood-supply of the common bile-duct and its relationship to the duodenum. *Br. J. Surg.* **43**, 75–80.

MCMASTER P., HERBERTSON B., CUSICK C. et al. (1978) Biliary sludging following liver transplantation in man. *Transplantation* **25**, 56–62.

MICHELS N. A. (1962) The anatomic variations of the arterial pancreaticoduodenal arcades: their import in regional resection involving the gallbladder, bile ducts, liver, pancreas and parts of the small and large intestines. *J. Int. Coll. Surg.* **37**, 13–40.

MONGÉ J. J., JUDD E. S. and GAGE R. P. (1964) Radical pancreatoduodenectomy: a 22-year experience with complications, mortality rate and survival rate. *Ann. Surg.* **160**, 711–722.

MUNKÁCSI I. and SIKLÓS I. (1960) Blood supply of the common bile duct. *Acta Morph. Hung.* **10**, 179–187.

NORTHOVER J. and TERBLANCHE J. (1978) Bile duct blood supply: its importance in human liver transplantation. *Transplantation* **26**, 67–69.

NORTHOVER J. M. A., WILLIAMS E. D. F. and TERBLANCHE J. (1979) The investigation of small vessel anatomy by scanning electron microscopy of resin casts: a description of the technique and examples of its use in the study of the microvasculature of the peritoneum and the bile duct wall. *J. Anat.* (In the press.)

PARKE W. W., MICHELS N. A. and GHOSH G. M. (1963) Blood supply of the common bile duct. *Surg. Gynecol. Obstet.* **117**, 47–55.

PFÖRRINGER L. (1971) Die arterielle Versorgung des Ductus choledochus. *Acta Anat.* **79**, 389–408.

RAINS A. J. H. (1959) Biliary obstruction in the region of the porta hepatis. *Ann. R. Coll. Surg. Engl.* **24**, 69–100.

RANGA V. V. and ANDRONESCU P. (1966) Die Gefabe des Ductus choledochus. *Anat. Anz.* **118**, 516–521.

SHAPIRO A. L. and ROBILLARD G. L. (1948) The arterial supply of the common and hepatic bile ducts with reference to the problems of common duct injury and repair. *Surgery* **23**, 1–11.

STARZL T. E., PUTNUM C. W., WEIL R. et al. (1976) Orthotopic liver transplantation in ninety-three patients. *Surg. Gynecol. Obstet.* **142**, 487–505.

TOMPSETT D. H. (1970) *Anatomical Techniques*, 2nd ed. Edinburgh, Livingstone.

WILLIAMS R., SMITH M., SHILKIN K. B. et al. (1973) Liver transplantation in man: the frequency of rejection, biliary tract complications, and recurrence of malignancy based on an analysis of 26 cases. *Gastroenterology* **64**, 1026–1048.

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A comparison of xenon-133 clearance with electromagnetic flowmeters and an indicator dilution method for the measurement of liver blood flow

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SUMMARY

Measurement of liver blood flow has been carried out by three different methods in 14 dogs to assess the accuracy of xenon-133 clearance following portal vein injection.

Electromagnetic flowmetry with flow probes on the hepatic artery and portal vein resulted in a mean value of 121·9 ± 39·3 ml min^{-1} 100 g^{-1}. An indicator dilution study utilizing chromium-51-labelled red cells gave a mean value of 119·4 ± 31·4 ml min^{-1} 100 g^{-1} and the xenon-133 clearance following portal vein injection, 120·3 ± 33·8 ml min^{-1} 100 g^{-1}. One-way analysis of variance showed no statistically significant variation between these three groups. There was a close correlation between xenon-133 clearance and electromagnetic flowmetry and between xenon-133 clearance and the indicator dilution technique.

These data suggest that xenon-133 clearance following portal vein injection gives an accurate assessment of liver blood flow and this technique (as well as direct parenchymal injection) can be adapted for clinical use.

FOR several years the clearance of an inert radioactive gas has been used to measure blood flow through tissues. Recently this method, using xenon-133, has been adopted to determine hepatic blood flow (Birtch et al., 1967; Sherriff et al., 1977). The resulting clearance curves have a double exponential form, although recent work has suggested that only the initial fast component gives an indication of hepatic blood flow, while the slow component is due to extrahepatic sources (Darle, 1970; MacKenzie et al., 1976). Measurements of liver blood flow using the clearance of xenon-133 give an indication of nutritive perfusion and we have used this method in our studies on both normal liver and liver metastases (Sheriff et al., 1977).

Clearly it is important to ascertain that measurements obtained by clearance studies accurately reflect the flow throughout the whole liver and that the results obtained are comparable with those obtained by other methods. This study, carried out in the dog, compares the liver blood flow calculated from the clearance of xenon-133 with that derived from electromagnetic flowmeters and an indicator dilution technique. Clearance of xenon-133 was measured following injection into both the portal vein and the hepatic parenchyma. The technique of direct injection into the liver parenchyma has obvious clinical importance, since it is simple to perform and does not require access to either the portal vein or the hepatic artery. Previous reports have suggested that the technique is both reliable and reproducible (Gelin et al., 1968) but it has not been compared with the more conventional methods of blood flow measurement.

Materials and methods

Experiments were performed on 14 dogs (weighing between 15 and 20 kg). Anaesthesia was induced by intravenous injection of sodium pentobarbitone and, following endotracheal intubation, was maintained with nitrous oxide, oxygen and 0·5–1 per cent halothane. The dogs were ventilated in an open circuit. Saline solution was infused through the brachial vein.

Through a midline incision, the portal vein and hepatic artery were mobilized to ensure that at least 2 cm of each vessel were clearly visible. The portal vein was cannulated via the pancreatic vein.

The cranial mesenteric artery was cannulated via the femoral artery, and one hepatic vein, usually the left, was cannulated via the jugular vein.

Flow measurements

Electromagnetic flowmeter: Appropriate flow probes were attached around mobilized segments of the portal vein (above the junction with the pancreatic vein) and the hepatic artery. Care was taken to ensure that the probes fitted closely to the vessel without causing constriction (probes which are either too tight or too loose give false readings).

The probes were attached to a Biotronex Flowmeter (Model BL613 EZ–ZA) and flow in millilitres per minute through each vessel was read directly off the scale. Readings were taken at 2-min intervals. The results were expressed in ml/min for each vessel and in ml min^{-1} 100 g^{-1} wet weight of liver for the total hepatic blood flow.

Indicator dilution studies: The indicator used in these studies was autologous red blood cells, labelled with chromium-51 (^{51}Cr-RBCs). These were prepared according to the method of Wagner (1968) using 250 µCi of ^{51}Cr-sodium chromate in 15 ml of blank, autologous whole blood. The packed ^{51}Cr-RBCs were reconstituted to the original haematocrit of the dog with 0·9 per cent w/v saline. Then 2·7 ml of reconstituted blood was rapidly injected into the mesenteric artery through the cannula which was flushed through with 10 ml of saline. Immediately portal and hepatic venous blood samples were collected and collection continued at 1-s intervals on identical fraction collectors (LKB Redirac, modified) for 60 s. Aliquots of 0·4 ml were taken from the injection mixture to be used as a standard, and from each subsequent sample. These aliquots were counted for ^{51}Cr gamma activity on a Nuclear Chicago gamma counter (model no. 4233).

Xenon-133 studies: A collimated sodium iodide detector 2 in (5 cm) in diameter was positioned on a fixed stem so that the liver was in the field of view. Approximately 0·5 µCi of xenon-133 in 0·1–0·5 ml saline were injected into the portal vein cannula and flushed through with 10 ml saline. The clearance curve was recorded over a 10-min period on a pen recorder.

When residual activity had reached low levels, a further measurement of hepatic blood flow was obtained by direct parenchymal injection of xenon-133.

Liver function tests

The concentration of total protein, albumin, sodium, potassium and bilirubin was determined in the serum of all dogs. Serum activity of glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, alkaline phosphatase and glutamic dehydrogenase was also determined at the commencement of the study and dogs with abnormal liver function tests were excluded.

At the completion of the study the liver was removed and weighed to permit the expression of all flow in terms of liver weight (as ml min^{-1} 100 g^{-1}).

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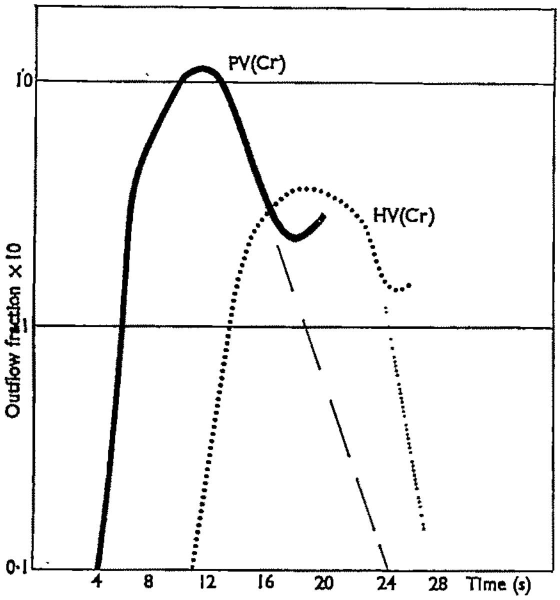

Fig. 1. A typical set of indicator dilution curves obtained from dog 12. PV (Cr) is the curve obtained for ^{51}Cr-labelled red blood cells (^{51}Cr-RBC) from the portal vein and HV (Cr) the curve obtained for ^{51}Cr-RBC from the hepatic vein.

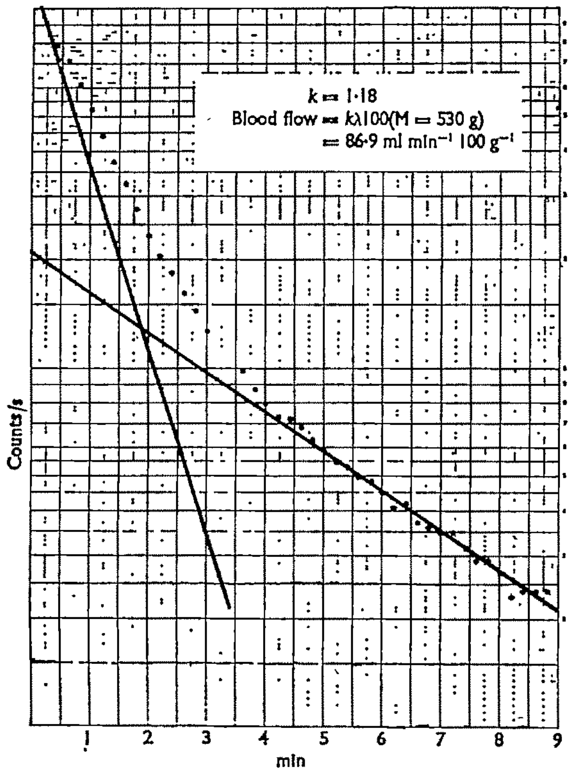

Fig. 2. Double exponential curve recorded following portal vein injection of xenon-133. The blood flow is calculated from the slope of the initial fast component.

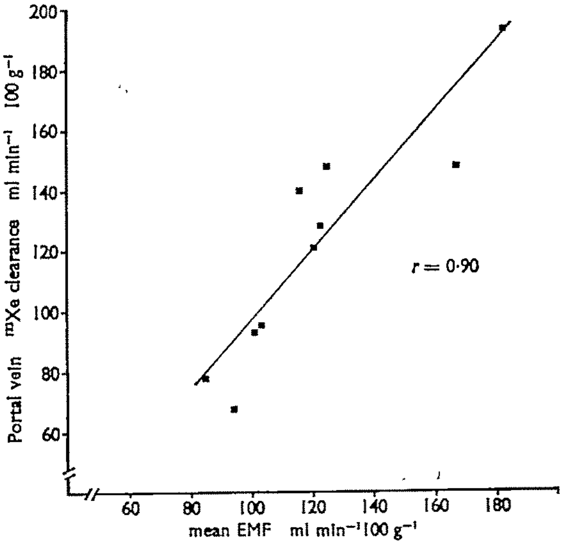

Fig. 3. Linear regression line for liver blood flow obtained by portal vein injection of xenon-133 and electromagnetic flowmetry.

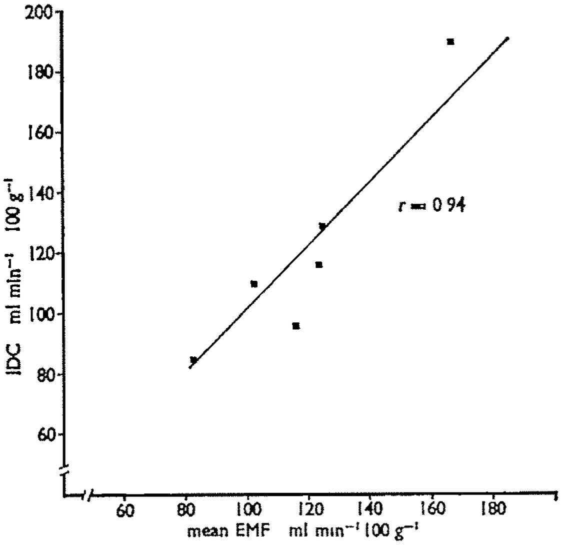

Fig. 4. Linear regression line for liver blood flow obtained by indicator dilution methods and electromagnetic flowmetry. The correlation coefficient (r) is 0·94, $P<0·001$.

Calculations of hepatic blood flow

Electromagnetic flowmeters: Flows for the portal vein and hepatic artery were read directly from the scale in ml/min and totalled to give hepatic blood flow.

Indicator dilution studies: Indicator dilution curves were constructed as graphs of outflow fraction × 10^3 against time where outflow fraction = (cpm/ml in sample)/(cpm/ml in standard). Portal and hepatic flow rates can be calculated directly from the area beneath the curves from the portal vein and hepatic vein respectively, from the formula:

$$\text{blood flow} = \frac{\text{cpm/ml standard}}{\text{(cpm/unit area)/unit time}} \times \text{area under curve.}$$

Xenon-133 clearance studies: The rate of disappearance of xenon-133, a rapidly diffusible gas, from a given tissue is dependent upon the blood flow through that tissue and the relative solubility of xenon-133 between the tissue and the blood (the partition coefficient). Thus, the clearance of the gas represents tissue (or nutritive) perfusion. The equation used to calculate tissue blood flow in ml min^{-1} 100 g^{-1} liver is blood flow $= k\lambda \times 100/\rho$, where k is the exponent of the exponential clearance curve (and is equal to $\ln 2/T_{\frac{1}{2}}$, where $T_{\frac{1}{2}}$ is the time taken for the liver activity to fall to half its initial value); λ is the partition coefficient for xenon, usually taken as 0·74 (Conn et al., 1961); and ρ is the density of liver tissue.

Results

Electromagnetic flowmetry

The mean values for total hepatic blood flow expressed in ml min^{-1} 100 g^{-1} are shown in *Table I*. These values varied from 78·8 to 200·0 ml min^{-1} 100 g^{-1} (mean 121·9 ± 39·3).

Indicator dilution studies

In 6 of the dogs studied, hepatic blood flow was measured by indicator dilution methods. A typical indicator dilution curve obtained from one of these dogs is shown in *Fig.* 1.

The values obtained by this method ranged from 84·3 to 189·3 ml min^{-1} 100 g^{-1} (mean 119·4 ± 31·4). These values are shown in *Table I*.

Xenon clearance

Portal vein injection: Liver blood flow values following intraportal injection were obtained in 12 dogs. In each dog a double exponential curve was obtained (*Fig.* 2). Liver blood flow was calculated by measuring the slope of the fast component.

A wide variation was observed between the dogs (range 68·2–193·4 ml min^{-1} 100 g^{-1}, mean 120·3 ± 33·8). The values obtained were compared with the simultaneously observed flowmeter and indicator dilution values and are shown in *Table I*.

Parenchymal injection: Values of liver blood flow following direct parenchymal injection were obtained in 8 dogs. The values obtained are shown in *Table I*. In one dog (dog 3, *see Table I*) a monoexponential clearance was obtained, but in the remainder the typical double exponential curve was apparent. The values obtained varied between 69·8 and 132·3 ml min^{-1} 100 g^{-1} (mean 89·7 ± 21·3).

Comparison of hepatic blood flows obtained by different methods

It can be seen that a very close correlation exists between the total hepatic blood flow measured by the clearance of a portal injection of xenon-133 and by the use of electromagnetic flowmeters ($r = 0·90$). The regression curve for these factors is shown in *Fig.* 3. There were also strong positive correlations between total hepatic blood flow measured by the indicator dilution technique and those measured by the use of electromagnetic flowmeters (*Fig.* 4) and the clearance of a portal injection of xenon-133 ($r = 0·94$ and 0·79 respectively). One-way analysis of variance shows no statistically significant variation between these three groups (degrees of freedom, 2·29; $F = 0·177$; $P < 0·05$).

Table I: LIVER BLOOD FLOW MEASUREMENTS OBTAINED BY DIFFERENT TECHNIQUES IN EACH DOG

	Xenon clearance				Liver
	PI	DI	EMF	IDC	weight (g)
Dog	($n = 14$)	($n = 10$)	($n = 13$)	($n = 7$)	($n = 14$)
1	168·0	—	200·0	—	227
2	93·0	86·9	100·1	—	530
3	91·4	93·8	98·1	—	480
4	120·5	—	120·3	—	305
5	91·0	84·5	88·2	—	494
6	78·0	—	83·7	84·2	338
7	—	75·1	78·8	—	368
8	147·9	76·2	126·7	127·7	366
9	147·9	69·8	167 9	189·3	393
10	95·6	—	109·2	109·3	374
11	193·4	132·3	195·1	—	371
12	128·0	127·8	123·1	115·9	448
13	85·2	75·5	—	114·3	484
14	68·2	75·4	94·2	95·4	436
Mean (±1 s.e.m.)					
	120·3	89·7	121·9	119·4	401·0
	±33·8	±21·3	±39·3	±31·4	±79·8

PI, Portal injection; DI, direct injection; EMF, electromagnetic flowmetry; IDC, indicator dilution technique.

All flow values are expressed as ml min^{-1} 100 g^{-1}.

Discussion

Measurement of liver blood flow by noting the clearance of xenon-133 following portal vein administration has been shown to be a useful technique both in animals (Darle et al., 1970) and in man (Sheriff et al., 1977). The clearance curve obtained is a double exponential, of which the initial fast component represents blood flow whereas the other components are probably extrahepatic in origin (MacKenzie et al., 1976; Leiberman et al., 1978). If this technique is to find a place in routine clinical assessment then it must be shown to compare favourably in reproducibility with other, more established techniques. This is particularly important since the counts obtained indicate clearance from, and therefore blood flow through, superficial tissue which may not necessarily be the same as total liver blood flow as measured by electromagnetic flowmetry and indicator dilution methods. These three methods of measurement of total hepatic blood flow depend on different physical principles.

Electromagnetic flowmeters measure changes in the electromagnetic field induced by, and directly proportional to, the flow of blood through a vessel. Flowmeters placed on the hepatic artery and portal vein give measures of portal venous and hepatic arterial flow and therefore of total liver blood flow.

The indicator dilution technique relies on the dilution of an inert indicator by the blood flowing through an organ. The blood flow is directly proportional to the degree of dilution of that indicator. Certain requirements have to be fulfilled for the use of any compound as an indicator in the measurement of hepatic blood flow (Reichman et al., 1958; Shoemaker et al., 1961; Huet et al., 1973): (*a*) the indicator must be conserved, i.e. not metabolized or excreted by the liver; (*b*) there must be no loss of indicator through extrahepatic shunts; (*c*) the indicator must be thoroughly mixed with blood before it reaches the sampling sites; (*d*) sampling must be of mixed venous blood; (*e*) intrahepatic circulation must be in a steady state.

These conditions are all fulfilled for the use of ^{51}Cr-RBCs in these experimental conditions. The injection of the indicator into the cranial mesenteric artery ensures thorough mixing in the mesenteric circulation (Huet et al., 1973), and sampling from the portal vein close to its bifurcation and from a large hepatic vein ensures that mixed venous blood is being sampled. Since this is so, the portal blood flow and total hepatic flow can be directly calculated from the areas under the portal vein curve and hepatic vein curve respectively.

The xenon-133 clearance technique measures the rate of removal of xenon-133 from a tissue by the passage of blood through it. The rate of clearance is proportional to the rate of flow through the tissue and can be used to measure regional or total blood flow directly in ml $\mathrm{min^{-1}}$ 100 $\mathrm{g^{-1}}$ of tissue. The measurement of flow in ml $\mathrm{min^{-1}}$ unit $\mathrm{weight^{-1}}$ eliminates the need for knowledge of liver weight and allows direct comparisons to be made between different subjects.

Total hepatic blood flow measured simultaneously by these three techniques gives values that are highly comparable. Since all three methods are based on different principles it would therefore seem that they accurately measure blood flow. Of the three methods, injection of xenon-133 into the portal vein is preferable in the clinical situation since it is rapid (taking a total of about 15 min) and relatively simple. The technique employing indicator dilution curves requires less specialized equipment but it does require cannulation of the portal vein, the hepatic vein and the superior mesenteric artery.

Electromagnetic flowmeters can only be used to measure total hepatic blood flow when the abdomen has been opened and cannot be applied for preoperative estimation.

In three dogs direct parenchymal injection of xenon-133 gave a significantly lower blood flow than that produced by the other methods. The theoretical slow diffusion effect due to the injection of a bolus of fluid directly into the parenchyma has been avoided by the use of very small volumes of xenon-133 (0·1 ml). In order to avoid any artificially slow clearance due to retained activity in the injection syringe, a fine needle was employed and removed directly after the injection.

It would seem more likely that the results of direct injection of xenon-133 do not correlate well with the other three methods because this indicator is applied at tissue level. The portal injection of xenon-133, the ^{51}Cr-RBCs and the electromagnetic flowmeters are not applied at tissue level, and therefore measure *total* hepatic flow, including any intrahepatic portavenous shunting that may occur. The inclusion of shunted flow will give a value for hepatic blood flow higher than actual tissue perfusion. Since a direct injection of xenon-133 is cleared only by blood perfusing the parenchyma, this method should avoid shunted flow and measure the 'nutritional' liver blood flow, i.e. that which comes in contact with the sinusoids. This theory is supported by the fact that all the values obtained from direct injection of xenon-133 are lower than those measured by other methods, and also by the correlation between the results of direct injections within the group of dogs.

In conclusion, it appears that xenon-133 clearance is the least invasive, simplest and quickest of the three techniques, and as such is the most suitable for clinical studies. It is also accurate, reproducible and measures total liver blood flow. We are at present using this technique prior to creating portasystemic shunts in patients with portal hypertension to assess its value as a predictive test of postoperative liver function.

References

BIRTCH A. G., CASEY B. H. and ZAKHEIM R. M. (1967) Hepatic blood flow measured by krypton-85 clearance technique. *Surgery* **62**, 174–180.

CONN H. L. (1961) Equilibrium distribution of radio-xenon in tissue. Xenon haemoglobin distribution curve. *J. Appl. Physiol.* **16**, 1065–1070.

DARLE N. (1970) Xenon-133 clearance and liver blood flow. An experimental study in the cat. *Acta Chir. Scand.* Suppl. 407, pp. 1–64.

GELIN L., LEWIS D. H. and NILSSON L. (1968) Liver blood flow in man during abdominal surgery. *Acta Hepatosplen.* **15**, 13–20.

HUET P. M., LAVOIE P. and VIAKER A. (1973) Simultaneous estimation of hepatic and portal blood flows by indicator dilution techniques. *J. Lab. Clin. Med.* **82**, 836–846.

LEIBERMAN D. P., MATHIE R. T., HARPER A. M. et al. (1978) An isotope clearance method for measurement of liver blood flow during portasystemic shunt in man. *Br. J. Surg.* **65**, 578–580.

MACKENZIE R. J., LEIBERMAN D. P., MATHIE R. T. et al. (1976) Liver blood flow measurement. The interpretation of xenon-133 clearance curves. *Acta Chir. Scand.* **142**, 519–525.

REICHMAN S., DAVIS W. D., STORASSTIL J. P. et al. (1958) Measurement of hepatic blood flow by indicator dilution technique. *J. Clin. Invest.* **37**, 1848–1856.

SHERRIFF S. B., SMART R. C. and TAYLOR I. (1977) Clinical study of liver blood flow in man measured by ^{133}Xe clearance after portal vein injection. *Gut* **18**, 1027–1031.

SHOEMAKER W. C., STEENBERG R. W., SMITH L. L. et al. (1961) Experimental evaluation of an indicator dilution technique for the estimation of hepatic blood flow. *J. Lab. Clin. Med.* **57**, 661–670.

WAGNER H. N. jun. (1968) Technical details of common procedures. In: *Principles of Nuclear Medicine.* Philadelphia, Saunders, pp. 832–858.

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Exploration of the common bile duct: a comparative study

K. D. VELLACOTT AND P. H. POWELL*

SUMMARY

The results of a retrospective comparative study of 122 patients who underwent explorations of the common bile duct in a district general hospital over a 5-year period are presented. Seventy-eight patients had a supraduodenal choledochotomy, 32 had a transduodenal sphincterotomy and 12 had a combination of both procedures.

Particular attention was paid to postoperative complications in relation to the grade of the surgeon performing the operation and also to the age of the patient.

A total of 78 (64 per cent) patients had definite stones in the common bile duct. Of these patients, 7 (9 per cent) were subsequently shown to have retained stones, all having been operated on by registrars. Registrars also did more negative explorations than consultants.

Nine patients (7·4 per cent) died, all but 1 of them being over the age of 70 and 4 of them having had a combined procedure.

We conclude that transduodenal exploration should be avoided in patients over 70, particularly when added to a supraduodenal exploration.

CHOLECYSTECTOMY is the commonest elective abdominal operation performed in this country and between 10 and 49 per cent of these patients will have their common bile ducts explored (Le Quesne, 1964). The usual method of exploring the common bile duct has been by a supraduodenal approach, opening the duct as it lies in the free border of the lesser omentum with subsequent closure around a T tube, and this remains the method of choice for most British surgeons. This method, however, is not without complications and attention has been drawn from time to time to its disadvantages, the major one being the relatively high incidence of retained stones, which varies between 4 and 22 per cent in different series (Way et al., 1972, Glenn, 1974; Corlette et al., 1978). It is also impossible to see the sphincter, and attempted blind dilatation may lead to a false passage.

A second method of exploration was first described by Kocher in 1895 and it involves a transduodenal approach with a sphincterotomy of the duodenal papilla. Advocates of this method have shown a lower incidence of retained stones, no evidence of papillary stenosis after the procedure and, though there is reflux in many cases, this was not associated with postoperative cholangitis (Peel et al., 1975). Critics of the method have suggested a higher incidence of pancreatitis after sphincterotomy.

A third method involves a combination of both approaches and is usually used where a supraduodenal approach has failed, owing to either a stricture at the lower end of the bile duct or an impacted stone. Recently it has been suggested that this combined approach should be used electively in certain selected patients who have multiple stones, residual stones after previous surgery, stricture at the papilla or impacted stones in the ampullary region (Aubrey and Edwards, 1978). The advantage of using the method electively would be that a protracted attempt at a supraduodenal exploration could be avoided.

This retrospective study was conducted in a district general hospital to compare the results after these three procedures and to relate the results to the grade of the surgeon performing the operation.

Patients and methods

Cheltenham General Hospital is a district hospital serving a population of 200 000. There are three general surgeons, two of whom use the supraduodenal method of exploration while the other uses the transduodenal approach preferentially. Each expected their junior staff to carry out similar procedures. During the 5-year period from 1973 to 1977, 630 cholecystectomies were performed. Of these patients, 126 (20 per cent) underwent explorations of the common bile duct. Four of these patients were lost to follow-up, so that 122 patients are included in the study.

Patients were seen routinely in the outpatients department after their operations and those with persisting symptoms had intravenous cholangiograms. Those patients who were symptom-free, and had been discharged from the outpatients clinic, were not followed up further.

The operations were carried out in a standard manner and all the patients had peroperative cholangiography. There were 90 patients who had supraduodenal explorations, including those who had an additional sphincterotomy, and these were all closed around a T tube. Fifty of the patients had on-table postexploratory T tube cholangiograms and all 90 had T tube cholangiograms on or about the tenth postoperative day. Both types of exploration were drained postoperatively. Choledochoduodenostomy was not performed.

The number of cases in each group and the grade of surgeon performing the operation are shown in *Table I*.

The ages of the patients ranged from 19 to 91 years with a mean age of 66. Women predominated in the ratio of 2 : 1 (female 84, male 38).

Table I: NUMBERS IN EACH GROUP AND GRADE OF SURGEON PERFORMING THE OPERATION

	Supraduodenal	Transduodenal	Combined
Consultant	40	21	6
Registrar	38	11	6
Total	78	32	12

Results

Of the 122 patients explored, 78 (64 per cent) had stones in the common bile duct, giving an incidence of 12 per cent for the whole group of 630 cholecystectomies. Twenty-seven (61 per cent) of the remaining 44 operations where no stones were found were performed by registrars. Reasons for these negative explorations were dilated common bile ducts with a history of previous jaundice (14), no flow into the duodenum (15) and filling defects seen on operative cholangiography (15). Three patients in whom no stones were found in the common bile duct died. One had a transduodenal sphincterotomy for a very dilated common bile duct and the other 2 had a

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Table II: MORTALITY

Age (yr)	Operation	Grade of surgeon	Cause of death
83	TD	Reg.	Ascending cholangitis
85	TD	Cons.	Cirrhosis and renal failure
91	SD	Reg.	Cardiac failure
77	TD & SD	Cons.	Hepato-renal failure
74	TD	Reg.	Myocardial infarction
75	SD	Reg.	Septicaemia
70	TD & SD	Cons.	Pancreatitis and pulmonary embolus
58	TD & SD	Cons.	Hepato-renal failure
74	TD & SD	Reg.	Hepato-renal failure

TD, Transduodenal; SD, supraduodenal.

Table III: MEAN AGES IN EACH GROUP AND MORTALITY IN PATIENTS OVER 70

	SD	TD	TD & SD
Mean age (yr)	63	67	67
Patients over 70	17	8	3
No. of deaths in patients over 70	2	3	3

SD, Supraduodenal; TD, transduodenal.

Table IV: COMPLICATIONS

	SD (*n* = 78)	TD (*n* = 32)	Combined (*n* = 12)
Pancreatitis	0	0	2
Biliary leak	1	0	3
Retained stone	6	0	1
Septicaemia	2	0	0
Renal failure	0	1	3
Ascending cholangitis	1	1	0
DVT	1	0	0
Pulmonary embolism	0	0	1
Intra-abdominal abscess	0	1	0
Wound infection	14	6	1
Myocardial infarction	0	1	0

SD, Supraduodenal; TD, transduodenal.

Table V: WOUND INFECTIONS

Operation	No.	%
Supraduodenal	14	18·4
Transduodenal	6	18·7
Combined	1	9·1

Table VI: LENGTH OF STAY IN HOSPITAL

Operation	Days
Supraduodenal	15
Transduodenal	16
Combined	19

combined procedure for apparent papillary stenosis. All 3 patients were jaundiced.

In the 504 patients who had a cholecystectomy without exploration of the common bile duct, there were 5 deaths (a mortality of 1 per cent); in the group of 122 patients studied there were 9 deaths (a mortality of 7·4 per cent). If the deaths of patients who had negative explorations are taken separately, then the mortality in the explored group with stones was 6 out of 78 (7·6 per cent) and in those with no stones in the ducts, 3 out of 44 (6·8 per cent).

There were 2 (2·5 per cent) deaths in the supraduodenal group, 3 (9·6 per cent), in the transduodenal group and 4 (33·3 per cent) in the combined group. All except one of these patients was over 70 years of age (*Table II*). Four patients who had advanced obstructive jaundice died of renal failure. The mean ages for each group and the mortality in patients over 70 is shown in *Table III*.

None of the 12 patients in the combined group had this procedure performed as an elective operation. Eleven patients had initial supraduodenal explorations, 4 patients having impacted stones which could not be removed from above, and 7 had tight papillae which would not permit the passage of a small dilator from above and showed no flow into the duodenum on cholangiography. The remaining patient had an attempted transduodenal exploration by a registrar, but the papilla could not be found and a supraduodenal exploration was performed.

There were 6 retained stones in the supraduodenal group (7·7 per cent) and 1 retained stone in the combined group demonstrated by postoperative T tube cholangiography (*Table IV*). No patient in the transduodenal group has developed any symptoms to suggest retained stones. Five of the patients had on-table post-exploratory T tube cholangiography at which the retained stones were not detected. Retrospective examination of these films showed the stones to have been demonstrated in 2 cases. One patient who did not have an on-table T tube cholangiogram had an initial negative exploration. Two patients had their retained stones removed by further surgery. One patient had an endoscopic sphincterotomy but developed a duodenal perforation and died after further surgery. The remaining 4 patients have developed no symptoms from their retained stones and are being kept under regular review as outpatients. If the negative explorations are excluded, the incidence of retained stones in this study is 7 out of 78 operations (9 per cent).

Wound infection was defined as the presence of pus and there was an overall incidence of 18·2 per cent. There was no significant difference between the transduodenal and supraduodenal groups, as shown in *Table V*. Prophylactic antibiotics were not used routinely.

The incidence of wound infection was less in the combined group but 3 of the patients in the group died within 1 week.

There was also no significant difference in the length of hospital stay between the supraduodenal and transduodenal group, but this was considerably longer in the combined group (*Table VI*).

Discussion

The exploration rate in this study was exactly 20 per cent and there was a very high mortality and morbidity in those patients who underwent a combined supraduodenal and transduodenal exploration. All of these patients except one initially had a supraduodenal exploration and was therefore subjected to protracted operations. It was in this group that the only 2 cases of pancreatitis occurred and the amount of instrumentation was probably responsible for this, though both patients had T tubes. Keighley and Graham (1973) found a high incidence of pancreatitis after explorations of the common bile duct, particularly in those who had had a combined supraduodenal and transduodenal approach. Pancreatitis occurred in all 4 cases quoted by them. A much lower incidence of clinical pancreatitis has been found by other authors (Peel et al., 1975; Aubrey and Edwards, 1978),

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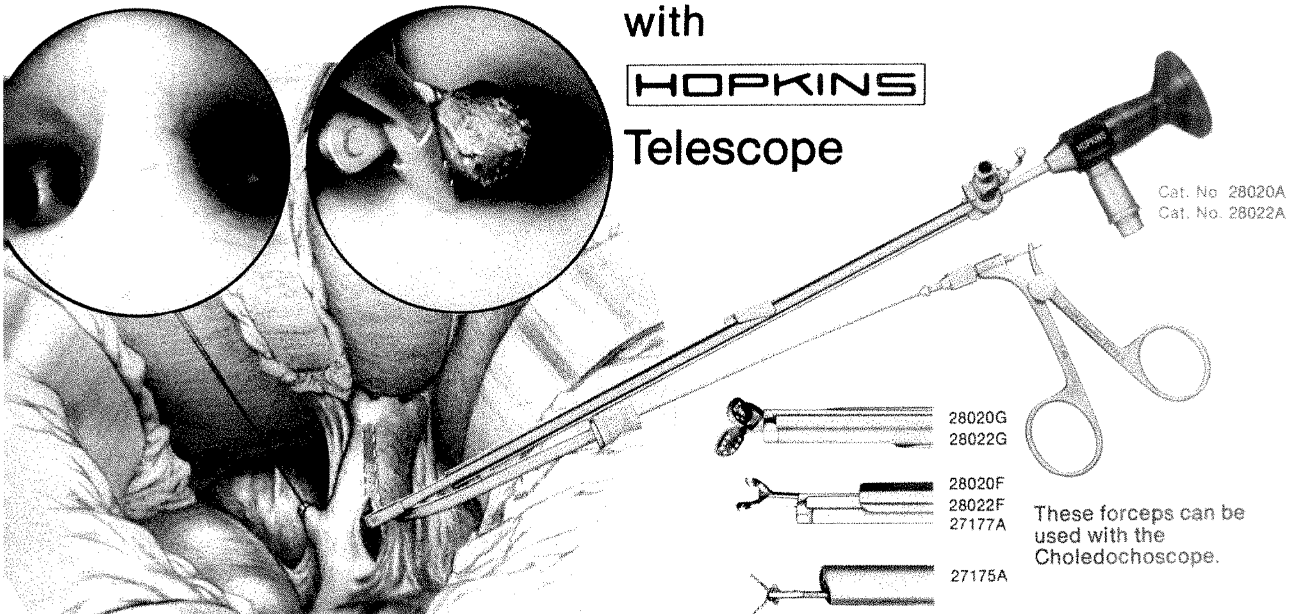

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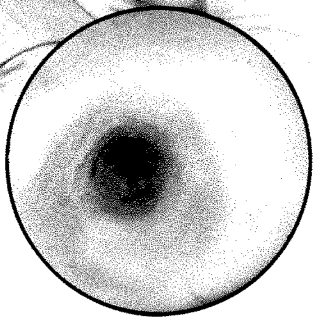

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References: Tompkins, R.K., Johnson, J., Storm, F.K., and Longmire, W.P.: Oper. Endo. in Mgmt. of Biliary Tract Neoplasms. Am. J. Sur., **132**:174-82, 1976. Shore, J.M.: Mod. Appr. to Managing Com. Duct Stones. Contempo. Sur., **9**:1976. Schein, C.J.: Infl. Of Choledochoscopy on Choice of Sur. Proc. Am. J. Sur., **130**:74-77, 1975.

Available Film: "Precise Biliary Explor." Shore, J.M., and Berci, G., Cedars-Sinai Med. Ctr., Los Angeles.

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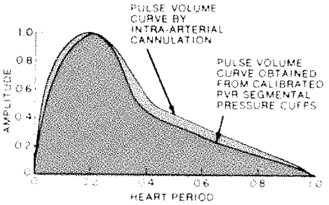

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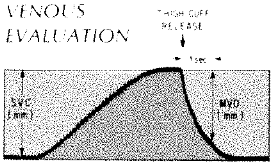

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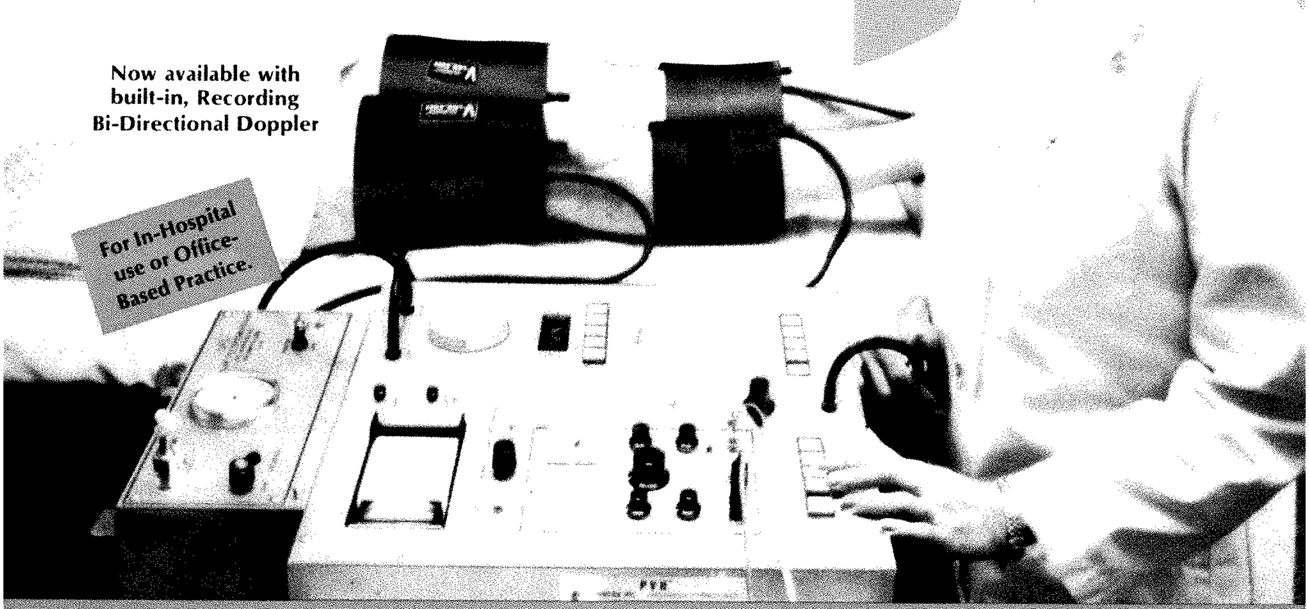

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A-I Stenosis ODS	YES	NO	NO	ABN	ABN	ABN	<50	5 (quick recovery)	Calf, Thigh, Buttocks
A-I Occlusion ODS	YES	NO	NO	ABN	ABN	ABN	<20	5	Calf, Thigh, Buttocks
SFA Occlusion (Low) No A-I Disease*	NO	YES	YES	NOR	ABN	ABN	20-50	4	Calf
SFA Occlusion (High) No A-I Disease*	YES	YES	YES	ABN	ABN	ABN	20-50	4	Calf, Lower Thigh
Combined Disease A-I + SFA	YES	YES	YES	ABN	ABN	ABN	<10	5	Calf, Thigh, Buttocks
Tibial Vessel Disease	NO	NO	YES	NOR	NOR	ABN	30-70	4	Foot, Ankle, Calf
Small Vessel Disease	NO	NO	NO	NOR	NOR	NOR**	—	—	—

A-I — *Aorto-iliac.* **ODS** — *Open Distal System.* **SFA** — *Superficial Femoral Artery.* * — *No Hemodynamically Significant A-I Disease Present.* † — *Values quoted are not absolute and are given as a guide.* ΔP_S —*Systolic Pressure Difference.* **ABN** — *Abnormal.* **NOR** — *Normal.* ** — **PVR** *recordings at transmetatarsal region and/or digits reduced.* P_S — *Systolic Pressure.*

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1) Schneider et al., Chirurg **47**, 185 (1976)
2) McMichan et al., Med. Welt **27**, 2331 (1976)

though the serum amylase may be raised without symptoms. This study showed no cases of clinical pancreatitis in either the supraduodenal or transduodenal group.

The grade of the surgeon performing the operation did not affect the mortality or morbidity in any group except in the case of retained stones, registrars having performed all of these operations. This would suggest that experience does play an important part in preventing this major complication of explorations of the common bile duct. Most general surgeons are unlikely to explore more than 12 common bile ducts in a year, so that it will take several years to become fully experienced in the technique. Most retained stones can be detected on postexploratory T tube cholangiography at the time of operation. The fact that 5 of the 7 cases with retained stones in this study had had postexploratory T tube cholangiograms illustrates that cholangiography is not infallible and is often extremely difficult to interpret. Corlette et al. (1978) showed an alarmingly high incidence of retained stones of 22 per cent. On retrospective examination of the postexploratory T tube cholangiograms, Corlette and colleagues found that in 16 of the 22 cases the stones were shown by the radiographs at the time of operation, but were overlooked. However, the examination may not always reveal retained stones and ducts can be explored in the presence of a normal cholangiogram and stones found (Way et al., 1972).

We were unable to demonstrate any significant complications attributable directly to T tube drainage. Ascending cholangitis occurred in 1 patient in the supraduodenal and 1 in the transduodenal group. However, there were 2 cases of septicaemia in the supraduodenal group (*Table IV*). Chande and Devitt (1973) suggested primary closure of the choledochotomy as they had shown a higher morbidity in patients with T tubes. With increasing success in dissolving stones with solutions infused down T tubes (Gardner et al., 1975; Chary, 1977) or by removal with a modified Dormia basket (Christiansen et al., 1978), we feel that T tube drainage should still be used after supraduodenal explorations. Endoscopists are also obtaining good results in the treatment of stones in the common bile duct by endoscopic sphincterotomy and basket extraction. The mortality rate for the procedure can be as low as 1·4 per cent (Safrany, 1978).

The mortality for patients over 70 years of age in the transduodenal and combined groups was very high. Johnson and Rains (1972) showed that in a series of 50 patients who had had a choledochoduodenostomy performed, 25 of whom were over 70, there were no postoperative deaths. Where exploration of the common bile duct by the supraduodenal method is proving difficult, and the operation likely to become prolonged, it would seem that a lower mortality could be obtained by doing a choledochoduodenostomy preferentially rather than risking a transduodenal sphincterotomy. Our findings would suggest that any transduodenal exploration should be avoided over the age of 70.

There was a surprisingly low incidence of thromboembolism, 1 case of deep vein thrombosis and 1 pulmonary embolus, though a proportion of the patients did receive low dose heparin treatment. In contrast, Keighley et al. (1976) showed a 12 per cent incidence of thromboembolism in patients with T tube drainage.

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References

AUBREY D. A. and EDWARDS J. L. (1978) The selective use of combined supraduodenal and transduodenal exploration of the common bile duct. *Br. J. Surg.* **65**, 246–251.

CHANDE S. and DEVITT J. E. (1973) T-tubes, the surgical amulet after choledochotomy. *Surg. Gynecol. Obstet.* **136**, 100–102.

CHARY S. (1977) Dissolution of retained stones using heparin. *Br. J. Surg.* **64**, 347–351.

CHRISTIANSEN L. A., NIELSON O. V. and EFSEN F. (1978) Non-operative treatment of retained bile duct calculi in patients with an indwelling T-tube. *Br. J. Surg.* **65**, 5581–5584.

CORLETTE M. B., SCHATZKI S. and ACKROYD F. (1978) Operative cholangiography and overlooked stones. *Arch. Surg.* **113**, 729–734.

GARDNER B., DENNIS C. R. and PATTI J. (1975) Current status of heparin dissolution of gallstones. *Am. J. Surg.* **130**, 293–295.

GLENN F. (1974) Retained calculi within the biliary ductal system. *Ann. Surg.* **179**, 528–537.

JOHNSON A. G. and RAINS A. J. H. (1972) Choledochoduodenostomy. A reappraisal of its indications based on a study of 64 patients. *Br. J. Surg.* **59**, 277–280.

KEIGHLEY M. R. B., BURDEN D. W., BADDELEY R. M. et al. (1976) Complications of supraduodenal choledochotomy: a comparison of three methods of management. *Br. J. Surg.* **63**, 754–758.

KEIGHLEY M. R. B. and GRAHAM N. G. (1973) The aetiology and prevention of pancreatitis following biliary tract operations. *Br. J. Surg.* **60**, 149–152.

KOCHER T. (1895) Correspondenz. *Bl. Schweiz. Aertze* **25**, 193.

LE QUESNE L. P. (1964) In: SMITH R. and SHERLOCK S. (ed.) *Surgery of the Gallbladder and Bile Ducts.* London, Butterworths, p. 122.

PEEL A. L. G., BOURKE J. B., HERMON-TAYLOR J. et al. (1975) How should the common bile duct be explored? *Ann. R. Coll. Surg. Engl.* **56**, 124–134.

SAFRANY L. (1978) Endoscopic treatment of biliary tract diseases. *Lancet* **2**, 983–985.

WAY L. W., ADMIRAND W. H. and DUNPHY J. E. (1972) Management of choledocholithiasis. *Ann. Surg.* **176**, 347–357.

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Renal function and other factors in obstructive jaundice

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SUMMARY

Renal function and other factors that possibly affect the outcome of operation were measured in 24 patients with obstructive jaundice and in 15 non-jaundiced controls. The preoperative features that were associated with a poor postoperative recovery from obstructive jaundice were a raised serum fibrinogen/fibrin degradation product concentration, infection, hypoalbuminaemia and a low glomerular filtration rate. Preoperative serum fibrinogen/fibrin degradation product concentrations were raised in 4 of the 6 jaundiced patients who died after surgery but in none of the controls, in whom there was no mortality.

In the jaundiced patients there was a greater incidence of postoperative renal impairment than in the controls. All patients were given mannitol during operation. Further mannitol was required after surgery in 13 of the 24 jaundiced patients in order to maintain urine flow rate despite adequate intravenous fluids being given. In contrast, only 1 of the 15 control patients required post-operative mannitol.

It is emphasized that repeated doses of mannitol can lead to a profound natriuresis and adequate intravenous saline should be given.

ACUTE renal failure after biliary tract surgery was first described in detail by two German surgeons, Clairmont and von Haberer, in 1911. They reported 5 women who died with acute uraemia shortly after cholecystectomy. Numerous descriptions of renal insufficiency after operations on patients with obstructive jaundice followed (Bartlett, 1933), the reported incidence varying from 6 per cent (Williams et al., 1960) to 12 per cent (Funck-Brentano et al., 1963). Uraemia was the commonest direct cause of death postoperatively in 350 patients with obstructive jaundice studied from 1947 to 1959 by Williams et al. (1960).

These findings led Dawson (1964) to suggest that the presence of obstructive jaundice might 'render the kidney more sensitive to decreased blood flow—that is, anoxia'. His observations on the structure and function of the rat kidney after temporary clamping of the renal artery showed that the incidence of both acute tubular necrosis and acute renal failure was higher in animals with obstructive jaundice. Intraperitoneal mannitol greatly reduced the effect (Dawson, 1964; Dawson and Stirling, 1964). Later studies on 7 patients with obstructive jaundice (Dawson, 1965) showed that a mannitol diuresis begun just before surgery and maintained for 2–3 days thereafter was associated with a less marked fall in creatinine clearance postoperatively.

The cause of the increased sensitivity of the kidney of a patient or experimental animal with jaundice remains uncertain; suggestions have included relative hypovolaemia (Williams et al., 1960; Cattell and Birnstingl, 1964), conjugated bilirubin (Baum et al., 1969), bile salts (Stewart and Cantarow, 1935; Aoyagi and Lowenstein, 1968), excessive quantities of vasodilator substance (Frank et al., 1946; Shorr et al., 1948), diminished renal cortical blood flow (Bloom et al., 1974) and increased sensitivity to the α-adrenergic effects of noradrenaline in obstructive jaundice (Bloom et al., 1975). Most recently the importance of renovascular fibrin deposition, perhaps related to a delayed clearance of endotoxin by the damaged liver, has been stressed (Wardle and Wright, 1970; Wilkinson et al., 1974; Wardle, 1975; Bailey, 1976).

In order to examine the relationship between obstructive jaundice, renal function and intravascular coagulation more closely, we have compared sequential observations in patients with obstructive jaundice to those in non-jaundiced control patients. As a marker for the presence of fibrin the estimation of fibrinogen/fibrin degradation products (FDP) was chosen. Serum FDP in most instances are formed from fibrin rather than fibrinogen substrate and thus reflect the extent of fibrin formation (Gallimore et al., 1972). Urinary FDP reflect mainly the formation and proteolysis of fibrin within the renal tract (Clarkson et al., 1971; Ekberg and Pandolfi, 1975).

We found that preoperative features with an adverse effect on postoperative recovery were a raised serum FDP concentration, infection, hypoalbuminaemia and a low glomerular filtration rate (GFR).

Patients and methods

A prospective study was made of 24 patients with obstructive jaundice (14 male, 10 female, mean age 61 years) and 15 non-jaundiced control patients (10 male, 5 female, mean age 49 years). admitted to the general surgical wards or to the University Department of Surgery, Glasgow Royal Infirmary, during 1974–5. Details of diagnosis and operations in both groups are given in *Tables I* and *II*. A malignant condition was present in 58 per cent of the jaundiced patients and 33 per cent of the control subjects.

Preoperatively, 24-h urine collections were carried out by spontaneous voiding and corresponding serum samples were obtained on at least two occasions for measurement of serum and urine creatinine and creatinine clearance (GFR), urinary sodium and potassium excretion rate and serum and urinary FDP levels. All the creatinine clearance levels have been corrected to the value for a body surface area of 1·73 m². Serum and urinary creatinine concentrations were obtained using the method of Hare (1950), electrolytes were measured on a direct-reading flame photometer (Instrumentation Laboratories Watertown, Mass., USA) and serum and urinary FDP concentrations were measured using Wellcome HA14 FDP test kits (Wellcome Laboratories, Beckenham, Kent), which are based on the red cell haemagglutination inhibition technique (Merskey et al., 1966). Urine was concentrated 25 times before assay using the Minicon B15 concentrator (Amicon Corp., Lexington, Mass., USA). The addition of the proteolytic inhibitor aprotinin (Trasylol, Bayer) did not alter serum FDP concentrations in a preliminary study, and therefore was not used. Routine examinations of full blood count, urea and electrolytes, liver function studies and blood pressure were made and urine and sputum cultures were obtained if there was any suggestion of infection. Maximum urinary concentrating ability was determined in 16 of the patients with obstructive jaundice and in 5 of the control subjects by measuring urine osmolality after a 12-h overnight fast and again 4 h after a subcutaneous

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injection of pitressin tannate in oil. Differences between jaundiced and control patients have been analysed using Student's *t* test (not significant if $P > 0{\cdot}05$).

Intravenous fluids (a minimum of 500 ml of isotonic saline and 500 ml of 5 per cent dextrose) were given for at least 12 h before operation together with mannitol 20 g intravenously 1 h before operation and a further 20 g during operation. Postoperatively, mannitol was given during the first 3 postoperative days (20 g i.v. over 15 min) to patients whose urine flow rate was less than 40 ml/h on two successive occasions despite adequate intravenous fluid therapy or to those who became hypotensive.

After surgery 24-h urine collections were made for at least 5 consecutive days and all preoperative serum and urine measurements were repeated. Patients with obstructive jaundice and some of the control subjects were catheterized for 2–3 days. Antibiotics were given only to control clinically significant infection. Bile cultures were obtained during operation in 12 of the 24 patients with obstructive jaundice.

Results

Before operation

Significant differences were found between the jaundiced and non-jaundiced groups of patients (*Table III*). Mean serum albumin concentration, mean haematocrit and mean urinary concentrating ability were significantly reduced in patients with obstructive jaundice. Serum FDP concentrations were raised (>10 μg/ml) in 9 of the 16 jaundiced patients in whom this was measured, but in none of the 13 control subjects (*Fig*. 1). This difference was not related to the incidence of preoperative infection, as judged by sputum culture, urine culture or bile culture, nor to the incidence of malignancy.

Fibrin degradation products were present in the urine of 6 of the 24 patients with obstructive jaundice compared with 1 of 14 control patients. In none did the excretion rate exceed 700 μg/d except in 1 jaundiced subject with a urinary tract infection (3·8 mg/d).

Mean GFR, sodium and potassium excretion rates did not differ significantly between the two groups—jaundice : control, GFR 81·2 ± 30·2 s.d. : 91·2 ± 22·7 s.d. ml min^{-1} 1·73 m^{-2}; sodium excretion, 101 ± 58 s.d. : 127 ± 52 s.d. mmol/24 h; potassium excretion, 34 ± 13 s.d. : 39 ± 13 s.d. mmol/24 h. However, there was a large variation in GFR in patients with obstructive jaundice (*Fig*. 2), not related to serum bilirubin concentration and in 5 jaundiced patients preoperative GFR was lower than in any of the control subjects and in 1 of these serum creatinine concentration was significantly raised. None gave a history of previous renal disease.

After surgery

Renal function: Acute renal failure, defined as an increase in serum creatinine concentration above the normal range, oliguria and a fall in GFR, was found within 2 weeks of operation in 4 patients with obstructive jaundice (*Fig*. 2), 3 of whom had had a low preoperative GFR and 1 of whom had had established renal insufficiency before surgery. None of the control patients had postoperative renal failure.

The percentage changes in urine flow rate, GFR and urinary sodium excretion during the first postoperative day as compared with the preoperative baseline levels are shown in *Table IV*. The variation in individual values for sodium excretion is plotted in *Fig*. 3 for the first 3 days. All patients had received mannitol before and during operation. Thirteen of the jaundiced patients required further mannitol postoperatively (jaundice group B in *Table IV* and *Fig*. 3) because of oliguria despite intravenous fluids. Only 1 of the control subjects required mannitol and this patient has not been included in the analysis (*Fig*. 3).

Table I: DIAGNOSIS AND OPERATION IN 24 PATIENTS WITH OBSTRUCTIVE JAUNDICE

No.	Diagnosis	Operation
9	Ca pancreas	Cholecystoenterostomy (5) Pancreaticoduodenectomy (2) Choledochoduodenostomy (1) Laparotomy (1)
3	Ca common bile duct	Laparotomy (1) Cholecystoenterostomy (2)
1	Ca common hepatic duct	Hepaticodochocholecystostomy
1	Ca gallbladder	Cholecystectomy
5	Cholelithiasis	Cholecystectomy and exploration of CBD (3) Choledochojejunostomy (2)
3	Stricture	Hepaticojejunostomy (1) Choledochojejunostomy (1) Hepaticoduodenostomy with U tube (1)
1	Mucocoele of gallbladder with external compression of CBD	Cholecystectomy
1	Cholangitis	Laparotomy

Figures in parentheses refer to number of patients.
Ca, Carcinoma; CBD, common bile duct.

Table II: DIAGNOSIS AND OPERATION IN 15 NON-JAUNDICED CONTROL PATIENTS

No.	Diagnosis	Operation
7	Duodenal ulcer	Partial gastrectomy, vagotomy (3) Gastroenterostomy, vagotomy (3) Pyloroplasty, vagotomy (1)
3	Ca pancreas	Pancreaticoduodenectomy (3)
2	Cholelithiasis	Cholecystectomy (2)
1	Ca stomach	Partial gastrectomy
1	Ca colon	Sigmoid resection
1	Chronic pancreatitis, post-cholecystectomy stricture	Pancreaticoduodenectomy

Figures in parentheses refer to number of patients.
Ca, carcinoma.

Table III: PREOPERATIVE FEATURES (mean ± s.d.)

	Haematocrit (%)	Serum albumin (g/l)	Serum FDP (>10 μg/ml)
Jaundice	36·1 (22) ±4·6	32·1 (22) ±6·3	9 (16)
P	<0·001	<0·02	—
Control	42·7 (14) ±4 1	38·0 (10) ±4·1	0 (13)

Figures in parentheses refer to number of patients.

Table IV: MEAN PERCENTAGE CHANGE IN URINE FLOW RATE, GFR AND URINARY SODIUM EXCRETION DURING FIRST POSTOPERATIVE DAY

	Control	Jaundiced A	Jaundiced B
Urine flow rate	↑ 88·7	↑ 16·5	↑ 20
GFR	↓ 1·2	↓ 3·3	↑ 16 9
Sodium excretion	↓ 12·4	↓ 7·9	↓ 11·2

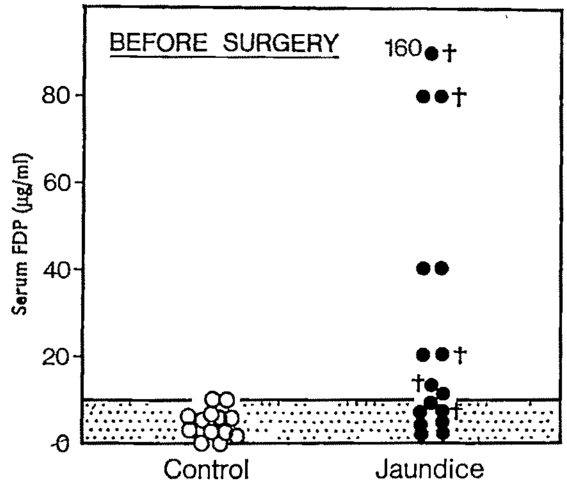

Fig. 1. Serum fibrinogen degradation product (FDP) concentration (µg/ml) before operation in 16 patients with obstructive jaundice and in 13 control patients. Values of less than 10 µg/ml have been accepted as within the normal range for healthy subjects. Patients dying within 2 weeks of operation are marked †.

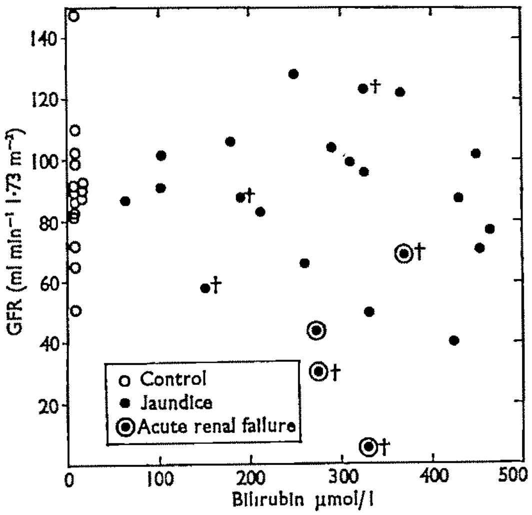

Fig. 2. Relationship of GFR (ml min^{-1} 1·73 m^{-2}) and serum bilirubin concentration (µmol/l) before operation to incidence of acute renal failure and/or death (†) within the first 2 postoperative weeks.

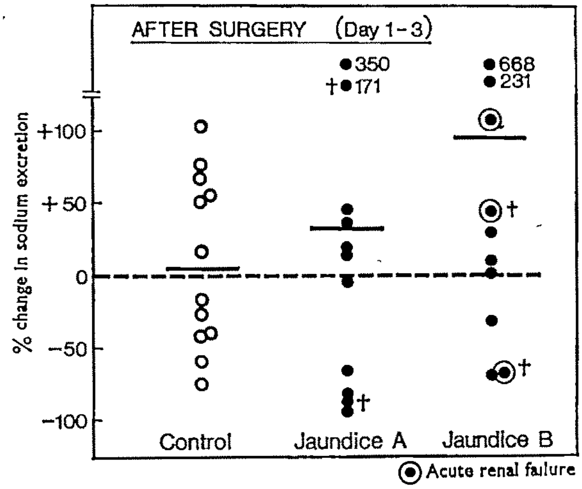

Fig. 3. Percentage change in sodium excretion during the first 3 postoperative days in 12 control subjects and 21 patients with obstructive jaundice. Control subjects and jaundice group A received mannitol only before and during surgery, while jaundice group B received further mannitiol over the first 2 postoperative days. The mean value for each group is represented by the horizontal line.

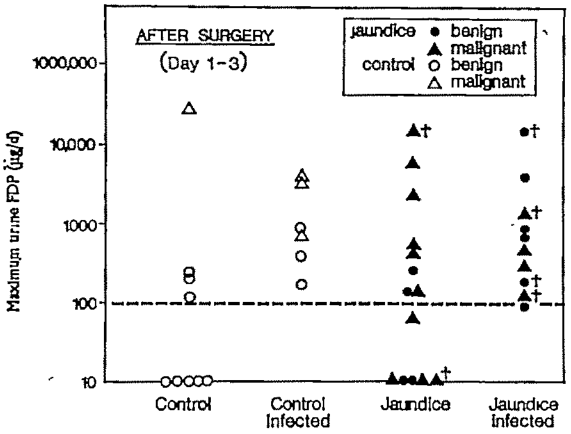

Fig. 4. Maximum urine FDP excretion rate (µg/d, logarithmic scale) during the first 3 postoperative days in control and jaundice patients with benign or malignant disease and with or without infection. The † indicates death within 2 weeks of operation. The broken line indicates the approximate upper limit of normal (100 µg/d).

The changes in urine flow rate and GFR were similar in all three groups; there was a diuresis but little alteration in mean GFR. In 18 out of the 24 patients with obstructive jaundice (75 per cent) GFR fell at least once within the first 3 postoperative days. GFR fell in 7 out of 14 control patients (50 per cent). In obstructive jaundice the mean maximum percentage fall in GFR was 35·7 ± 18·7 per cent ($n = 18$) and in the control group it was 52·5 ± 16·4 per cent ($n = 7$).

Sodium excretion fell during the first postoperative day in all patients despite the use of mannitol and intravenous fluids (*Table IV*). A natriuresis occurred during the next 2 days, however, in the patients with obstructive jaundice, especially in those given postoperative mannitol (*Fig.* 3, jaundice B).

Bile was taken for culture during operation in 12 patients with obstructive jaundice. A positive result was found in 3 patients, all of whom had gallstones and/or stricture of the common bile duct.

Deaths: Six of the 24 patients with obstructive jaundice died within 2 weeks of operation but none of the control patients; in 4 patients death was due to overwhelming infection, in 1 to uraemia and infection, while the final patient succumbed to a pancreatic carcinoma following laparotomy. Serum FDP concentrations before operation were measured in 4 of the 6 who died and were more than 10 µg/ml in all of them; in contrast, none of the control patients had elevated preoperative serum FDP levels. Forty per cent of the surviving jaundiced group also had raised preoperative serum FDP concentrations (*Fig.* 1).

FDP levels: Serum and urinary FDP levels rose after surgery in both jaundiced and control patients. Serum FDP concentrations increased significantly over the preoperative value in approximately 25 per cent in both groups (4 out of 14 jaundiced patients, 3 out of 12 control patients). These increases were associated with severe infection (5 patients) or postoperative haemorrhage (2 patients). A fall in GFR occurred in all of the jaundiced patients and in 1 of the controls, in whom a postoperative rise in serum FDP was seen.

Urinary FDP levels rose in 15 out of the 24 jaundiced subjects after operation and in 10 of 15 control subjects. A marked increase in the urinary FDP excretion rate was associated with severe infection such as bacteraemia or cholangitis in both groups (*Fig.* 4). There was no correlation between the presence of FDP in the blood and urine, very high levels of urinary FDP appearing in the urine at times when the serum FDP concentrations were not raised and vice versa. There was also no correlation between the urinary FDP excretion rate and change in GFR postoperatively. In 1 patient, however, a 22-year-old girl having undergone removal of a large mucocoele of the gallbladder, an episode of acute blood loss was associated with a sharp fall in GFR and a concomitant rise in urinary FDP excretion, which fell again as GFR rose 24 h later.

Discussion

It is widely accepted that there is an increased incidence of renal impairment in jaundiced patients, particularly after surgery or shock. Patients with resultant 'hepatorenal failure' seldom recover (Conn, 1973). We, therefore, set out to study the reasons why patients with obstructive jaundice might be particularly at risk of developing acute renal failure and what might be done to help them.

This report emphasizes two features of the problem. First, the preoperative features that were associated with a poor postoperative recovery from obstructive jaundice: these appear to be infection, hypoalbuminaemia, a low GFR and, most interestingly, a raised serum FDP concentration. This last factor was above control values in all 4 of the patients who died and in whom it had been measured.

Second, renal function can be well maintained postoperatively in patients with obstructive jaundice provided that adequate intravenous fluids and mannitol are given. The use of mannitol in obstructive jaundice, however, is associated with a marked natriuresis on days 2–3 postoperatively.

The association between raised preoperative FDP levels and a poor postoperative prognosis may help in the prediction of high risk patients, although the underlying mechanisms causing the FDP rise are not clear. It is known that ill patients with systemic complications have raised serum FDP levels (Wood et al., 1972) and that some of these FDP may be derived from fibrin within thrombi or pulmonary emboli (Ruckley et al., 1970). Alternatively, the FDP may be the end-product of a low-grade process of intravascular coagulation, triggered by stimuli such as bacteraemia or endotoxaemia (Merskey et al., 1967; Colman et al., 1972; Levin, 1973; Müller-Berghaus et al., 1976).

It is known that hepatic disease favours intravascular coagulation due to impaired clearance of activated coagulation enzymes and plasminogen activation (Deykin, 1966). In this situation, the jaundiced patients would be at greater risk than the non-jaundiced ones. A further source of FDP might be fibrinogen or fibrin laid down around areas of inflammation at extravascular sites and reabsorbed after digestion by the lymphatic system. The mechanism of so-called 'disseminated extravascular coagulation' has been suggested by several investigators (Straub, 1977), by which FDP, derived from extravascular fibrinogen or fibrin, are reabsorbed into the circulation via the lymphatic system.

The urine FDP levels did not correlate well with serum FDP, in keeping with observations that most urine FDP are derived locally from the kidney rather than reflecting filtered serum FDP (Clarkson et al., 1971; Ekberg and Pandolfi, 1975). The fact that jaundiced patients had significantly higher preoperative FDP levels in both serum and urine may again reflect the increased tendency to fibrin formation in jaundice. In view of the findings of Clarkson et al. (1971) that no significant increase in urinary tract FDP excretion occurred as a result of renal tract infection, it is unlikely that this was the cause of the rise in urine FDP in patients with obstructive jaundice. It must be remembered that patients labelled 'infected' in *Fig.* 4 had evidence of either systemic or urinary infections; only 3 of the 16 had urinary infections, detected by urine culture, at the time of urine FDP estimation, the other patients having bacteraemia or cholangitis. Thus, there is a suggestion, as seen in *Fig.* 4, that systemic infection is associated with increased urine FDP excretion, in that only non-infected patients had normal urine FDP levels. Whether the infective process is the direct cause of renal fibrin deposition and urine FDP production is uncertain.

The possibility that intravascular coagulation in jaundice might precipitate renal failure by means of glomerular fibrin deposition has been explored (Wardle and Wright, 1970; Wilkinson et al., 1974; Wardle, 1975; Bailey, 1976). Using the Limulus assay (Reinhold and Fine, 1971), Wardle (1975) detected postoperative endotoxaemia in 73 per cent of patients with obstructive jaundice. Similarly, Bailey (1976) found peripheral endotoxaemia in just over half of his jaundiced patients postoperatively. We did not measure blood endotoxin levels in this study and the significance of our observation remains speculative.

With regard to the postoperative progress of our patients with obstructive jaundice, 4 had evidence of significant renal impairment while this was present in none of the control subjects, although the distribution of malignant disease and infection was roughly comparable in both. All received a similar volume of intravenous saline and dextrose and a similar quantity of intravenous mannitol before and during surgery. While the pattern of changes in urine flow rate, glomerular filtration rate and sodium excretion was roughly comparable in both the control and the jaundiced subjects, two points should be made. First, nearly half of the jaundiced patients required further mannitol postoperatively in order to maintain their urine flow rate, despite apparently adequate intravenous fluids. Secondly, patients given large loads of mannitol had a profound natriuresis during the second and third postoperative days. It is, therefore, important that such patients are given adequate saline postoperatively.

Mannitol is a powerful osmotic diuretic, inhibiting the reabsorption of water and sodium in the proximal tubule and the loop of Henle, thus promoting both a diuresis and a natriuresis in association with volume expansion. There is an increase in total renal blood flow and in medullary blood flow even at very low perfusion pressures (Wendling et al., 1969; Gennari and Kassirer, 1974). Of greater importance, perhaps, is the fact that mannitol appears to have the ability to prevent endothelial cell swelling during hypoperfusion, thus stopping the 'no reflow phenomenon' (Flores et al., 1972). These properties have led to the widespread use of mannitol as a prophylactic agent during potential renal ischaemia and as a substance capable of reversing incipient acute renal failure (Barry et al., 1961; Eliahou, 1964; Luke et al., 1970; Morris et al., 1972). Our patients received a relatively small quantity of mannitol compared with that suggested by Dawson in 1965. Despite this, renal function was well maintained postoperatively in most patients.

Our observations emphasize the importance of prompt diagnosis and relief of bile duct obstruction. Preoperative investigative techniques such as ultrasound, percutaneous transhepatic cholangiography and endoscopic retrograde cholangiopancreatography now allow correct diagnosis in almost all patients (Blumgart, 1978). In many patients a period of biliary drainage will permit recovery of liver function with improvement in nutrition, coagulation disorders and renal function and possibly increased resistance to endotoxaemia (Blumgart, 1978) before proceeding to major resectional surgery. Even bypass operations, however, are associated with an appreciable mortality of approximately 20 per cent (Nakase et al., 1977). Careful preoperative assessment of nutritional and coagulation status, as well as of renal function, is required.

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References

AOYAGI J. and LOWENSTEIN L. M. (1968) The effect of bile acids and renal ischaemia in renal function. *J. Lab. Clin. Med.* **71**, 686–692.

BAILEY M. E. (1976) Endotoxin, bile salts and renal function in obstructive jaundice. *Br. J. Surg.* **63**, 774–778.

BARRY K. G., COHEN A. and LE BLANC P. (1961) Mannitolisation. 1. Prevention and therapy of oliguria associated with cross-clamping of the abdominal aorta. *Surgery* **50**, 335–340.

BARTLETT W. (1933) Renal complications of biliary tract infection. *Surg. Gynecol. Obstet.* **56**, 1080–1095.

BAUM M., STIRLING G. A. and DAWSON J. L. (1969) Further study into obstructive jaundice and ischaemic renal damage. *Br. Med. J.* **2**, 229–231.

BLOOM D., BOMZON L., ROSENDORFF C. et al. (1974) The effect of obstructive jaundice on renal blood flow. *Clin. Sci.* **47**, 3P–4P.

BLOOM D., MCCALDEN T. A. and ROSENDORFF C. (1975) Effects of jaundiced plasma on vascular sensitivity to noradrenaline. *Kidney International* **8**, 149–157.

BLUMGART L. H. (1978) Biliary tract obstruction: new approaches to old problems. *Am. J. Surg.* **135**, 19–31.

CATTELL W. R. and BIRNSTINGL M. (1964) Renal function in obstructive jaundice. *Br. J. Surg.* **51**, 72.

CLAIRMONT P. and VON HABERER H. (1911) Ueber Anurie nach Gallenstein operationen. *Mitt. Grenzgeb. Med. Chir.* **22**, 159–172.

CLARKSON A. R., MACDONALD W. K., PETRIE J. J. B. et al. (1971) Serum and urinary fibrin/fibrinogen degradation products in glomerulonephritis. *Br. Med. J.* **3**, 447–451.

COLMAN R. W., ROBBOY S. and MINNA J. D. (1972) Disseminated intravascular coagulation: an approach. *Am. J. Med.* **52**, 679–689.

CONN H. O. (1973) A rational approach to the hepatorenal syndrome. *Gastroenterology* **65**, 321–340.

DAWSON J. L. (1964) Jaundice and anoxic renal damage: protective effect of mannitol. *Br. Med. J.* **1**, 810–811.

DAWSON J. L. (1965) Postoperative renal function in obstructive jaundice: effect of a mannitol diuresis. *Br. Med. J.* **1**, 82–86.

DAWSON J. L. and STIRLING G. A. (1964) Protective effect of mannitol on anoxic jaundiced kidneys. *Arch. Pathol.* **78**, 254–259.

DEYKIN D. (1966) The role of the liver in serum induced hypercoagulability. *J. Clin. Invest.* **45**, 256–263.

EKBERG M. and PANDOLFI M. (1975) Origin of urinary fibrin/fibrinogen degradation products in glomerulonephritis. *Br. Med. J.* **2**, 17–19.

ELIAHOU H. E. (1964) Mannitol therapy in oliguria of acute onset. *Br. Med. J.* **1**, 807–809.

FLORES J., DIBONA D. R., BECK C. H. et al. (1972) The role of cell swelling in ischemic renal damage and the protective effect of hypertonic solute. *J. Clin. Invest.* **51**, 118–126.

FRANK H. A., SELIGMAN A. M. and FINE J. (1946) Traumatic shock: XIII. The prevention of irreversibility in haemorrhagic shock by the vivi-perfusion of the liver. *J. Clin. Invest* **25**, 22–29.

FUNCK-BRENTANO J. L., MERY J. P., VANTELON J. et al. (1963) Les insuffisances rénales aigues de l'angiocholite urémigène (18 observations personelles). *Presse Méd.* **71**, 1039–1042.

GALLIMORE M. J., TYLER H. M. and SHAW J. T. B. (1972) The origin of fibrin breakdown products and the interpretation of their appearance in the circulation. *J. Clin. Pathol.* **25**, 185–190.

GENNARI F. J. and KASSIRER J. P. (1974) Osmotic diuresis. *N. Engl. J. Med.* **291**, 714–720.

HARE R. S. (1950) Endogenous creatinine in serum and urine. *Proc. Soc. Exp. Biol. Med.* **74**, 148–151.

LEVIN J. (1973) Endotoxin and endotoxemia. *N. Engl. J. Med.* **288**, 1297–1298.

LUKE R. G., BRIGGS J. D., ALLISON M. E. M. et al. (1970) Factors determining response to mannitol in acute renal failure. *Am. J. Med. Sci.* **259**, 168–174.

MERSKEY C. J., JOHNSON A. J., KLEINER G. J. et al. (1967) The defibrination syndrome: clinical features and laboratory diagnosis. *Br. J. Haematol.* **13**, 528–549.

MERSKEY C., KLEINER G. J. and JOHNSON A. J. (1966) Quantitative estimation of split products of fibrinogen in human serum: relationship to diagnosis and treatment. *Blood* **28**, 1–18.

MORRIS C. R., ALEXANDER E. A., BRUNS F. J. et al. (1972) Restoration and maintenance of glomerular filtration by mannitol during hypoperfusion of the kidney. *J. Clin. Invest.* **51**, 1555–1564.

MULLER-BERGHAUS G., BOHN E. and HÖBEL A. (1976) Activation of intravascular coagulation by endotoxin. The significance of granulocytes and platelets. *Br. J. Haematol.* **33**, 213–220.

NAKASE A., MAUTSUMOTO Y., UCHIDA K. et al. (1977) Surgical treatment of cancer of the pancreas and periampullary region. *Ann. Surg.* **185**, 52–57.

REINHOLD R. B. and FINE J. (1971) A technique for quantitative measurement of endotoxin in human plasma. *Proc. Soc. Exp. Biol.* **137**, 334–340.

RUCKLEY C. V., DAS P. C., LEITCH A. G. et al. (1970) Serum fibrin/fibrinogen degradation products associated with postoperative pulmonary embolus and venous thrombosis. *Br. Med. J.* **4**, 395–398.

SHORR E., ZWEIFACH B. W. and FURCHGOTT F. (1948) Hepato-renal factors in circulatory homeostasis: III. The influence of hormonal factors of hepato-renal origin on the vascular reactions to hemorrhage. *Ann. NY Acad. Sci.* 49, 571–592.

STEWART H. L. and CANTAROW A. (1935) Renal lesions following injection of sodium dihydrocholate in animals with and without biliary stasis. *Arch. Pathol.* 20, 866–881.

STRAUB P. W. (1977) Diffuse intravascular coagulation in liver disease. *Semin. Thromb. Hemostasis* 4, 29–39.

WARDLE E. N. (1975) Endotoxaemia and the pathogenesis of acute renal failure. *Q. J. Med.* 44, 389–398.

WARDLE E. N. and WRIGHT N. A. (1970) Endotoxin and acute renal failure associated with obstructive jaundice. *Br. Med. J.* 4, 472–474.

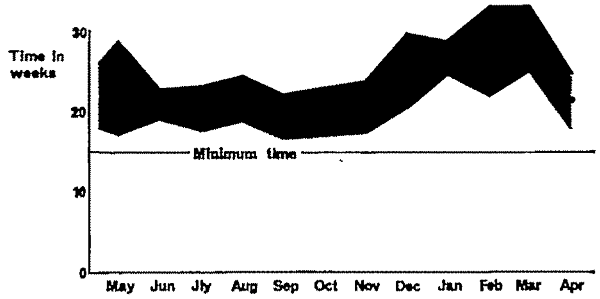
WENDLING M. G., ECKSTEIN J. W. and ABBOUD F. M. (1969) Effects of mannitol on the renal circulation. *J. Lab. Clin. Med.* 74, 541–547.

WILKINSON S. P., ARROYO V., GAZZARD B. G. et al. (1974) Relation of renal impairment and haemorrhagic diathesis to endotoxaemia in fulminant hepatic failure. *Lancet* 1, 521–524.

WILLIAMS R. D., ELLIOT D. W. and ZOLLINGER R. W. (1960) The effect of hypotension in obstructive jaundice. *Arch. Surg.* 81, 335–340.

WOOD E. H., PRENTICE C. R. M. and MCNICOL G. P. (1972) Association of fibrinogen–fibrin-related antigen with postoperative deep-vein thrombosis and systemic complications. *Lancet* 1, 166–169.

Paper accepted 10 November 1978.



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Acute pancreatitis in Hong Kong

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SUMMARY

A series of 311 Chinese patients with acute pancreatitis admitted to Queen Mary Hospital, Hong Kong, over a 10-year period is reviewed. Biliary tract disease was associated with pancreatitis in 52·4 per cent of patients and 77·9 per cent of them had stones, mud or parasites in the common bile duct. Fever and jaundice were present in 55 per cent and 41·2 per cent of patients respectively. Because of the prevalence of recurrent pyogenic cholangitis among the indigenous population, emergency operation, with the aim of common duct decompression, was conducted in 54·3 per cent of patients during the acute episode, with a mortality rate of 14·8 per cent. Five of 142 patients (3·5 per cent) died whilst on conservative treatment and all 5 had haemorrhagic pancreatitis. The overall mortality rate was 9·6 per cent. Exploration of the common bile duct, which was carried out in 57·4 per cent of patients in the acute phase, was not associated with a higher mortality than when laparotomy alone was performed, and 19 patients had sphincteroplasty without any death. Subtotal pancreatectomy was performed in 2 patients with haemorrhagic pancreatitis with 1 death.

MORTALITY rates of acute pancreatitis reported from different countries vary quite widely. These variations have been attributed to associated aetiological factors in different proportions as well as to different racial compositions (Albo et al., 1963; Marks and Banks, 1963; Mayday and Pheils, 1970; Imrie, 1974; Olsen, 1974). However, even in the same country, mortality rates have varied depending on whether the study was carried out prospectively or retrospectively (Trapnell and Anderson, 1967; Imrie, 1974; Trapnell et al., 1974; Imrie and Whyte, 1975). Furthermore, the mortality rate associated with operations in the acute phase has been claimed to be prohibitively high (Imrie, 1974), or not different from that associated with conservative treatment (Trapnell and Anderson, 1967; Trapnell, 1974).

In Hong Kong, where biliary tract disease is common among the indigenous Chinese population, it has been our practice to perform an early operation on patients with acute pancreatitis.

We present here the results of a retrospective study of 311 cases of acute pancreatitis with particular reference to the associated aetiological factors and the results of early surgical intervention.

Patients and methods

Patients

Over a 10-year period from 1967 to 1976 311 patients with acute pancreatitis were admitted to the University Surgical Unit, Queen Mary Hospital, Hong Kong. There were 123 males and 188 females. Age incidence is shown in *Fig.* 1 and the range was 7–86 years with a mean of 47·6 years.

Diagnostic criteria: Patients who presented with a clinical history consistent with acute pancreatitis and confirmed by the finding of a serum amylase of 1000 Somogyi units or more, or urinary diastase of 60 Wohlgemuth units or more were included in this study. Patients with operative or post-mortem findings of acute pancreatitis were also included.

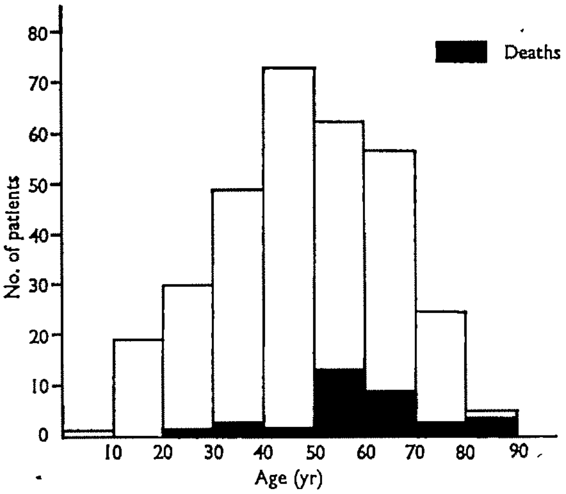

Fig. 1. Age and mortality of cases of acute pancreatitis.

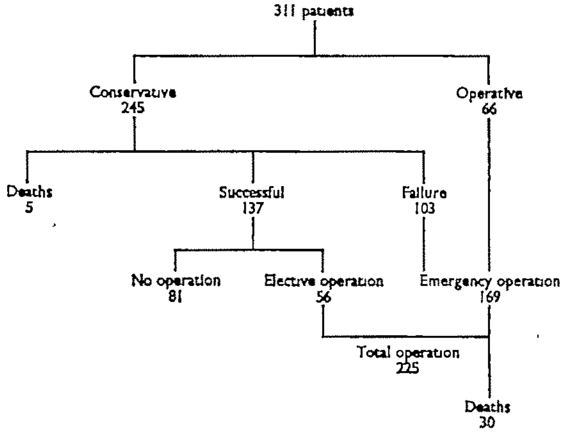

Fig. 2. Summary of treatment and results.

Biliary disease was accepted as an associated factor when confirmation was obtained at operation or at post-mortem examination, or when radiological investigations at least 6 weeks after an acute episode demonstrated stones in the biliary system. All patients successfully treated without operation were investigated radiologically for biliary tract disease with oral cholecystography and intravenous cholangiography.

Patients who drank more than 300 ml of spirits daily for more than 10 years and who suffered from an attack within 36 h of the last bout of drinking were regarded as suffering from alcoholic pancreatitis.

Shock was diagnosed when the blood pressure dropped to 80 mmHg or below at any stage of the acute attack before or after the institution of conservative therapy.

Respiratory failure was diagnosed in any patient who had tachypnoea in spite of oxygen therapy and who showed radiological evidence of diffuse infiltration in both lung fields; or

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when arterial oxygen estimations showed a level of 70 mmHg or less.

Renal failure was present when a rise in blood urea of over 20 SI units failed to respond to adequate fluid replacement.

Ileus was present when nasogastric aspiration yielded 500 ml or more per day for 5 days or more and when there was no clinical or radiological evidence of mechanical obstruction.

Haemorrhagic pancreatitis was diagnosed only at operation or post-mortem examination when there was gross retroperitoneal haemorrhage, usually in association with bloody intraperitoneal fluid and fat necrosis. Microscopic evidence of haemorrhage alone was not included.

Associated aetiological factors: The commonest associated condition was biliary tract disease (*Table I*). This accounted for 163 (52·4 per cent) of our patients and 127 (77·9 per cent) had stones, mud or parasites in the common bile duct. Alcoholism was associated in 15·1 per cent and trauma in 7·4 per cent of patients. In 75 patients (24·1 per cent) no associated factors were evident.

Number of attacks on presentation: This presentation represented a first attack in 73·2 per cent of the patients, a second attack in 12·1 per cent, a third attack in 4·8 per cent and 3·9 per cent presented in their sixth or more attack, the maximum being a fourteenth attack in one patient.

Clinical features: Pain was the universal symptom. Fever and jaundice were present in 55 and 41·2 per cent respectively and 10·6 per cent of patients presented in or developed shock in the course of their acute attack. Peritonitis was present in 29·6 per cent and an abdominal mass was found in 5·1 per cent.

Plain X-ray of abdomen: This investigation was of little value in the diagnosis of acute pancreatitis. Gallstones were seen in 4·2 per cent, a sentinel loop in 2·6 per cent and gas in the biliary tree in 0·6 per cent.

Treatment

Management of acute attack: Initial management included nasogastric aspiration, intravenous fluid replacement, analgesics (usually pethidine) and antibiotics (usually ampicillin). Atropine and Trasylol were given to 22 and 9 patients respectively in the past, but these two drugs were not used in recent years.

Patients in shock were monitored by measurement of central venous pressure, hourly urinary output and regular estimations of arterial gases. Plasma infusion and, occasionally, blood were given until blood pressure and urinary output were satisfactory.

Patients who were jaundiced, in shock, or had signs of peritonitis or in whom other diagnoses (particularly recurrent pyogenic cholangitis) were suspected were operated on after initial resuscitative treatment. Since recurrent pyogenic cholangitis may be associated with shock from septicaemia, or peritonitis without clinical jaundice, patients in shock or who had peritonitis during their acute attack were invariably explored, even though the diagnosis of acute pancreatitis was established biochemically. Thus the suspicion of cholangitis either as the primary or an additional diagnosis was the indication for the vast majority of emergency operations. Conservative treatment was deemed to have failed in patients who continued to have severe symptoms or became shocked, or developed signs of peritonitis or jaundice. These patients were also subjected to emergency operations.

Emergency operations were performed on 66 patients (21·2 per cent) soon after admission (*Fig.* 2). Conservative treatment on the remaining 245 patients was successful in 137 (55·9 per cent). One hundred and three patients (42 per cent) failed to respond to conservative treatment and underwent emergency operations up to 10 days after admission. In all, 169 patients (54·3 per cent) were operated on during the course of their acute attack. The indications for operation are shown in *Table II*.

Of the 137 patients successfully managed conservatively, elective operations were performed in 56 (40·9 per cent) because of radiologically demonstrated biliary tract disease (51 patients), or because of development of pancreatic pseudocyst (5 patients). Five patients who had biliary tract disease initially refused operation but because of recurrent attacks subsequently underwent surgery. Eighty-one patients (59·1 per cent) were not operated on. Thus, in total, 225 patients (72·3 per cent) underwent operative treatment either as an emergency or elective procedure.

At operation during the acute attack the pancreas was found to be oedematous in 115 patients (68 per cent), there was haemorrhage in 25 and in 29 patients the gland showed localized necrosis with abscess formation. In 109 of these 169 patients (64·5 per cent) biliary tract disease was present.

Operations performed during acute attack: The procedures carried out and the mortality associated with each procedure are shown in *Table III*. Laparotomy alone or with biopsy or with drainage of the pancreatic bed was performed in 32·5 per cent of patients. Biliary tract operations were performed in all the remainder except 7. The commonest biliary operation was exploration of the common bile duct (57·4 per cent) with or

Table I: ASSOCIATED AETIOLOGICAL FACTORS

		No. of patients
Biliary tract disease		163 (52·4)
Gallstones	36 (11·5)	
RPC	77 (24·8)	
Gallstones + RPC	50 (16·0)	
Alcoholism		47 (15·1)
Traumatic		23 (7·4)
Postoperative complication	16 (5·1)	
External injury	7 (2·3)	
Pregnancy and post-partum		3 (1·0)
Idiopathic		75 (24·1)
Total		311 (100·0)

RPC, Recurrent pyogenic cholangitis.
Figures in parentheses are percentages.

Table II: INDICATIONS FOR EMERGENCY OPERATION

	No.	%
Generalized peritonitis and uncertain diagnosis*	64	37·9
Jaundice with peritonitis	40	23·7
Shock with peritonitis	33	19·5
Persistent pain	27	16·0
Epigastric mass	5	2·9
Total	169	100·0

* Many suspected to have recurrent pyogenic cholangitis.

Table III: OPERATIONS PERFORMED IN ACUTE ATTACK AND MORTALITY

		No.	%		Died	MR*
Laparotomy		55	32·5		8	14·5
Alone	19			3		
With biopsy of omentum	16			2		
With biopsy of pancreas	6			0		
With drainage of pancreatic bed	14			3		
Exploration of common bile duct		97	57·4		14	14·9
Alone	47			11		
With cholecystectomy	31			2		
With cholecystectomy and sphincteroplasty	10			0		
With cholecystostomy	4			1		
With sphincteroplasty	5			0		
Cholecystectomy		4			0	
Cholecystostomy		2			1	
Sphincteroplasty		4			0	
Pancreatectomy		4			2	
Gastrocystostomy		3			0	
Total		169	100·0		25	14·8

* Mortality rate of procedure.

Table IV: PANCREATECTOMY IN ACUTE PANCREATITIS

Sex/Age	Aetiological factor	Pathology found	Operation performed	Result	Complication	Cause of death
M/50	Postoperative	Oedematous pancreatitis with abscess	Distal pancreatectomy	Died on day 2	Massive gastrointestinal bleeding	Sepsis and gastrointestinal bleeding
F/52	Idiopathic	Oedematous pancreatitis with pseudocyst	Partial pancreatectomy	Alive 5 yr	Nil	—
F/67	Idiopathic	Haemorrhagic pancreatitis	Subtotal pancreatectomy	Died on day 17	Gastric fistula, diabetes, hypocalcaemia, respiratory failure	Sepsis, respiratory failure
M/61	Biliary	Haemorrhagic pancreatitis	Subtotal pancreatectomy	Alive 2 yr	Persistent sinus for 3 mth, diabetes	—

Table V: COMPLICATIONS OF THE DISEASE

	No.	%
Ileus	81	26·0
Shock	33	10·6
Septicaemia	19	6·1
Pancreatic abscess	13	4·2
Hypocalcaemia with tetany	8	2·6
Pancreatic pseudocyst	5	1·6
Gastrointestinal bleeding	2	0·6

Table VI: NON-FATAL POSTOPERATIVE COMPLICATIONS

	No.	%
Wound infection	9	5·3
Subphrenic abscess	8	4·7
Residual ductal stone	8	4·7
Chest infection	5	2·9
Discharging sinus	4	2·4
Gastrointestinal bleeding	2	1·2
Renal failure	2	1·2
Intestinal fistula	1	0·6
Burst abdomen	1	0·6

Table VII: CAUSES OF DEATH IN THE OPERATED GROUP

	No.	%
Septicaemia	16	9·5
Peritonitis	14	8·3
Respiratory failure	14	8·3
Shock	13	7·7
Renal failure	11	6·5
Subphrenic abscess	6	3·5
Gastrointestinal bleeding	2	1·2
Intestinal fistula	1	0·6
Myocardial infarction	1	0·6

Table VIII: DEATHS AND ASSOCIATED AETIOLOGICAL FACTORS

	No. of deaths	% of total	Overall incidence (%)
Biliary	18	60·0	52·4
Gallstones	3		
RPC	10		
Gallstones + RPC	5		
Alcoholic	7	23·4	15·1
Traumatic	1	3·3	7·4
Pregnancy and post-partum	1	3·3	1·0
Idiopathic	3	10·0	24·1
Total	30	100·0	

RPC, Recurrent pyogenic cholangitis.

without an added procedure. Sphincteroplasty was carried out in 19 patients (11·2 per cent). Four patients had pancreatectomies and their clinical summaries are shown in *Table IV*.

Results

Complications of the disease and operations

The complications of the disease are shown in *Table V*. Since over half (54·3 per cent) of our patients were operated on during the acute attack, this Table represents complications that were present on admission or which developed in the course of non-operative treatment. Since the non-operated group was selected on the basis of a clinically mild attack, a relatively low incidence of complications may therefore be expected. Non-fatal postoperative complications are shown in *Table VI*. Some of these complications may be the result of the disease rather than of the operation, and the incidence of complications of the disease may well have been greater if fewer patients had undergone operation.

Respiratory failure occurred in 19 patients and was a significant factor in the death of 14. Renal failure was present in 13 patients and was a contributory cause of death in 11.

Mortality rates

There were 30 deaths (9·6 per cent) in this series. In the group operated on during the acute attack, the mortality rate was 25 out of 169 (14·8 per cent). In the non-operated group, it was 5 out of 142 (3·5 per cent). In the operated group, those who underwent exploration of the common bile duct did not suffer a higher mortality than those who had exploratory laparotomy alone (*Table III*), and 19 patients had sphincteroplasty without a death. Two of 4 patients who had a pancreatectomy died. The causes of death in the operated group are shown in *Table VII*.

The deaths tabulated according to aetiological factors and compared with the overall incidence of each aetiological factor are shown in *Table VIII*. The mean age of the 30 patients who died was 59 years, which was 11·4 years more than the mean age for the whole series. Only 4 deaths occurred in the under-50 age group (2·4 per cent). In the over-50 age group the mortality rate was 26 out of 144 (18·1 per cent).

At operation or post-mortem, the pancreas in the 30 cases who died was seen to be haemorrhagic in 23, showing localized necrosis with abscess in 3 and an oedematous gland in 4. Conversely, when an oedematous pancreas was found at operation the mortality was 4 out of 115 (3·5 per cent), which is the same as in the conservatively treated group. However, when localized necrosis with abscess formation was present

Table IX: MORTALITY OF OPERATIVE AND NON-OPERATIVE MANAGEMENT IN FOUR SERIES

	Bristol (1950–61)*			Glasgow (1960–70)†			Glasgow (1971–2)‡			Hong Kong (1967–76)§		
		Deaths			Deaths			Deaths			Deaths	
Treatment	*n*	*n*	%	*n*	*n*	%	*n*	*n*	%	*n*	*n*	%
Operative	91	21	23·1	41	15	36·6	11	5	45·5	169	25	14·8
Non-operative	233	55	23·6	86	9	10·5	67	4	6·0	142	5	3·5
Overall result	324	76	23·4	127	24	18·9	78	9	11·5	311	30	9·6

* Trapnell and Anderson (1967); † Imrie (1974); ‡ Imrie and Whyte (1975); § Present series.

the mortality rose to 3 out of 29 (10·3 per cent), and in those with haemorrhagic pancreatitis the mortality was 72 per cent.

The mortality rates of operative and non-operative management in this series are compared with those in three British series in *Table IX*.

Acute haemorrhagic pancreatitis

Although the exact incidence of this more severe form of pancreatitis in any reported series is unknown (but estimated to be between 10 and 25 per cent; Glazer, 1975), the mortality rate of haemorrhagic pancreatitis, when diagnosed at operation, was very high. In 169 emergency operations during the acute attack, 25 cases of haemorrhagic pancreatitis were found and 18 of them subsequently died (72 per cent). The 5 deaths in the conservatively treated group were all found to have haemorrhagic pancreatitis at post-mortem. Subtotal pancreatectomy was performed in 2 patients with 1 death.

Late results

Of the 311 patients in this series, 107 were not available for follow-up study (30 died in the acute episode, 9 died from other causes after discharge from hospital and 68 defaulted follow-up). Of the remaining 204 patients, 199 (92·6 per cent) were symptom-free and 15 (7·4 per cent) had further attacks. Six of these 15 had biliary tract diseases demonstrated but refused surgery. Five subsequently were operated on and were free of further symptoms. Two patients had attacks after biliary tract surgery but have now been without symptoms for 3 and 8 years respectively. Seven patients had no biliary tract diseases but suffered recurrent attacks; 4 of these 7 patients had biliary surgery without arrest of subsequent attacks.

Discussion

Associated aetiological factors

The incidences of associated aetiological factors in our series are almost identical to those reported in recent British series (Imrie, 1974; Trapnell, 1974), but contrast significantly with American, Australian and South African series (Marks and Banks, 1963; Barraclough and Coupland, 1972; Olsen, 1974) where alcohol was demonstrated to be the cause in half or more of the patients with acute pancreatitis. Biliary tract disease was shown to be the most commonly associated condition in our series (52·4 per cent), although this proved not to be as high as we had previously suspected. Our incidence of unknown causes is high, and is a feature of a retrospective study (Imrie, 1974) as compared with a prospective one (Imrie and Whyte, 1975). Quite likely, more patients in the idiopathic group would be classified as alcoholics if a more searching history was obtained, and the incidence of biliary tract disease would be higher if more refined investigations were performed on patients who recovered from conservative treatment. Only one patient with alcoholic pancreatitis had gallstones, a rare association, also shown by Barraclough and Coupland (1972) though denied by Mayday and Pheils (1970) and Olsen (1974).

In our series, the incidence of ductal stones in patients with biliary tract disease was 77·9 per cent, which was much higher than that reported by Barraclough and Coupland (1972) (11·1 per cent) and by Imrie (1974) (20 per cent). This is reflected in the presentation of a large number of our patients with fever and jaundice from cholangitis. This high incidence of ductal stones encouraged us to operate early in patients with suspected biliary tract disease. Since ductal stones may pass through the ampulla (Acosta and Ledesma, 1974), and in some cases possibly after initiating an attack of pancreatitis, the incidence of ductal stones in reported series is probably underestimated. Furthermore, as radiological diagnosis of biliary tract disease may have false negative results, the true incidence of biliary tract disease may be even higher.

Mortality rate

Mortality rates reported in British series with similar incidences of aetiological factors have been higher than ours: Trapnell and Anderson (1967), 23·4 per cent; Imrie (1974), 18·9 per cent; present series, 9·8 per cent. However, a recent prospective study by Imrie and Whyte (1975) showed that there is a decline in mortality rates (to 11·5 per cent), and the reasons for this have been attributed by the authors to a lower incidence of diagnosis by laparotomy than in the retrospective studies, earlier diagnosis because of clinical awareness, improved methods of serum and urine amylase estimations, an appreciation of the risk from operations and improved care from personal interest in the condition. Since these factors are not features of our retrospective study, it must be concluded that our low mortality rate reflected a different natural history of the disease in our Chinese patients. Similar low mortality rates have been reported by Albo et al. (1963) (11 per cent), Louw et al. (1967) (12 per cent) and Olsen (1974) (6 per cent), where the incidence of alcoholic pancreatitis was high.

Mortality associated with operation in the acute phase of pancreatitis varies greatly in different reports. Those in favour of early operation (Trapnell, 1966; Louw et al., 1967; Kune, 1968; Diaco et al., 1969; Barraclough and Coupland, 1972) claimed that there was no added risk when laparotomy and simple remedial surgery were carried out. On the other hand, Imrie (1974) and Imrie and Whyte (1975), in both retrospective and prospective studies, have shown the mortality rate of operation to be 3½ and 7½ times respectively that of conservative treatment. Our series also demonstrated a greater than fourfold increase in mortality rate associated with operation.

This high mortality is related to the many patients in our series who were operated on in shock and with cholangitis, which gave rise to deaths from infections and respiratory and renal failure.

The high mortality rate associated with acute haemorrhagic pancreatitis is reflected in our series. Since the true incidence of haemorrhagic pancreatitis in any series of acute pancreatitis is not known, reported mortality rates of between 40 per cent and 82 per cent (Kaplan et al., 1964; Kune, 1968; Nugent and Zuberi, 1968; Jordan and Spjut, 1972) are only approximations. Of the 30 deaths in our series, 23 (76·7 per cent) had haemorrhagic pancreatitis. Since we had operated on about half of our patients during the acute attack (and operation was performed on those with severe disease), and since the incidence of operative diagnosis of haemorrhagic pancreatitis was only 14·8 per cent, it would appear that in our community the incidence of haemorrhagic pancreatitis is unlikely to exceed 10–15 per cent, which is within the range of 10–25 per cent estimated by Glazer (1975).

Operative management

We operated on 54·3 per cent of our patients in the acute phase because of the high incidence of biliary tract disease, especially the condition of recurrent pyogenic cholangitis (Ong, 1968), among the indigenous population. Many of these patients presented with or developed septicaemic shock from cholangitis. In addition, 12·5 per cent of the patients with recurrent pyogenic cholangitis also had pancreatitis. Thus, even when a diagnosis of acute pancreatitis is established biochemically, if there is any suspicion of cholangitis, such as jaundice, fever or chills, early surgical intervention is mandatory. When the serum amylase is not raised and cholangitis is suspected, the need for early operation is even more urgent as all the clinical features may be attributable to cholangitis. It is also our belief that when acute pancreatitis is associated with ductal stones, decompression of the bile duct may minimize the severity or reverse the progression of the disease. For these reasons, early operation was our choice of treatment unless the disease was clinically mild, there was a strong probability that alcohol was the cause or biliary tract disease could reasonably be excluded.

Common duct exploration was the procedure most frequently performed (57·4 per cent) and the mortality of this procedure did not differ from that of laparotomy alone. Although we were reluctant to perform sphincteroplasty in the acute phase because of the many recognized hazards (Anderson, 1965; Louw et al., 1967; Trapnell, 1972), this operation was carried out in 19 patients without complications or deaths. In each instance a stone was impacted at the ampulla, and we believe, as do Salzman and Bartlett (1963), that under these circumstances this operation is essential and can be performed without added risk to the patient.

Pancreatectomy for acute haemorrhagic pancreatitis has been advocated by Watts (1963), Hollender et al. (1969) and Guivarch et al. (1972). Although this is a severe operation in a critically ill patient, removal of the necrotic gland may offer these patients a small chance of recovery since the mortality of other forms of treatment is equally prohibitive. The rapid clinical improvement of the one patient in this series who survived subtotal pancreatectomy may indicate that in selected patients this course of treatment
appropriate one.

Our mortality rate in the operated gro
per cent is substantially higher than that i
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and Imrie (1974), could probably be reduc
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the mortality rate is not unduly high. This
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lethal procedure as it was once thought. It
undertaken if the diagnosis is in doubt
patient's condition deteriorates in spite o
conservative measures. This principle has
advocated by Anderson (1965), Zimberg (
Glazer (1975).

Our results show that patients with bi
disease who refuse surgery almost invari
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subsequent attacks, the risk of such
appears to be minimal. On the other ha
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References

ACOSTA J. M. and LEDESMA C. L. (1974) Gallstone mi
cause of acute pancreatitis. *N. Engl. J. Med.* 2

ALBO R., SILEN W. and GOLDMAN L. (1963) A cri
analysis of acute pancreatitis. *Arch. Surg.* **86,**

ANDERSON M. C. (1965) Surgical intervention in
creatitis. *Surg. Gynecol. Obstet.* **120,** 1301–13

BARRACLOUGH B. H. and COUPLAND G. A. E. (
pancreatitis: a review. *Aust. N.Z. J. Surg.* **41,**

DIACO J. F., HILLER L. D. and COPELAND E. M. (1969)
early diagnostic laparotomy in acute pancre
Gynecol. Obstet. **129,** 263–269.

GLAZER G. (1975) Haemorrhagic and necrotizing
Br. J. Surg. **63,** 169–176.

GUIVARCH M., BEAUFILS F., NEURY N. et al. (1972
surgery in necrotic pancreatitis. *J. Chirurgie*
479–492.

HOLLENDER L. F., GILLET M., SAVA G. et al. (1969)
operative pancreatitis: clinical study and pl
systematic intervention, with early pancrea
Chirurgie (Paris) **97,** 177–198.

IMRIE C. W. (1974) Observation on acute pancrea
Surg. **61,** 539–544.

IMRIE C. W. and WHYTE A. S. (1975) A prospecti
acute pancreatitis. *Br. J. Surg.* **63,** 490–494.

JORDON G. L. and SPJUT H. J. (1972) Hemorrhagic
Arch. Surg. **104,** 489–493.

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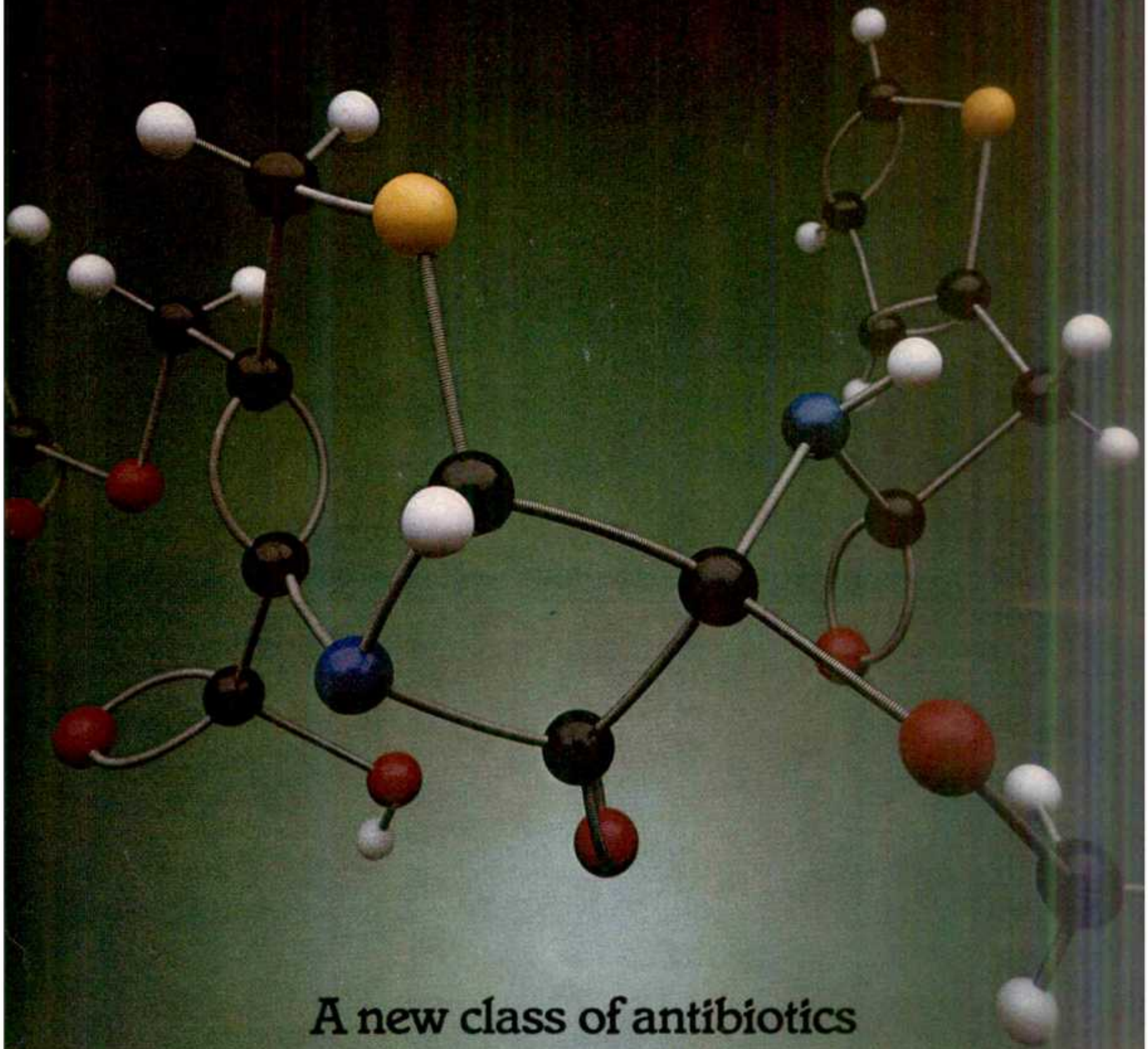

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A solution of 'Mefoxin' in Water for Injection BP may be added to the following solutions: 0.9% Sodium Chloride Injection BP, 5% or 10% Dextrose Injection BP, Dextrose and Sodium Chloride Injection (5%/0.9%, 5%/0.45%, or 4.3%/0.18%), Lactated Ringer's Injection USP, 5% Dextrose in Lactated Ringer's Injection, 5% or 10% invert sugar in water, 10% invert sugar in saline solution, 4.2% Sodium Bicarbonate Injection BP, M/6 Sodium Lactate Injection BP.

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Contra-indications

'Mefoxin' is contra-indicated in persons who have shown hypersensitivity to cefoxitin. In the absence of clinical experience, 'Mefoxin' should not be administered to patients who have shown hypersensitivity to cephalosporins.

Precautions

There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and other β-lactam antibiotics, penicillins, and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most β-lactam antibiotics.

Before therapy with 'Mefoxin', careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibiotics. 'Mefoxin' should be given cautiously to penicillin-allergic patients.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. If an allergic reaction to 'Mefoxin' occurs, the drug should be discontinued.

The total daily dosage should be reduced when 'Mefoxin' is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see 'Dosage and administration') because high and prolonged serum antibiotic concentrations can occur from usual doses.

Interference with laboratory tests

A false-positive reaction to glucose in the urine may occur with reducing substances but not with the use of specific glucose oxidase methods.

Use in pregnancy

Use of the drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the foetus due to 'Mefoxin'. There are no controlled studies with 'Mefoxin' in pregnant women.

Nursing mothers

'Mefoxin' is excreted in human milk.

Infants and children

Pending the outcome of clinical trials in progress, the conditions for use of 'Mefoxin' in infants and children remain to be defined.

Side effects

'Mefoxin' is generally well tolerated. Side effects rarely require stopping treatment and usually have been mild or transient.

Local reactions

Thrombophlebitis has occurred with intravenous administration. Pain induration and tenderness after intramuscular injections have been reported.

Allergic

Maculopapular rash, urticaria, pruritus, [illegible] and other allergic reactions have been noted rarely.

Gastro-intestinal

Diarrhoea has been reported rarely.

Blood

Transient leucopenia and neutropenia have been reported. Some individuals, particularly those with [illegible] positive direct Coombs tests during therapy [illegible]

Liver function

Transient elevations [illegible] alkaline phosphatase have been reported rarely.

Kidney

Elevations in serum creatinine and/or [illegible] been observed. The role of 'Mefoxin' in changes [illegible] is difficult to assess, since factors predisposing [illegible] or to impaired renal function usually have [illegible]

Presentation

In vials containing 1 g or 2 g of cefoxitin [illegible] gram of cefoxitin contains approximately [illegible] sodium.

Product licence numbers: 1 g 0025/[illegible]

Product authorisation numbers: 1 g [illegible]

Issued October 1978

Additional information is available to the medical profession on request.

Basic NHS cost is £4.47 [illegible] the 1 g vial [illegible] 94 for the 2 g vial.

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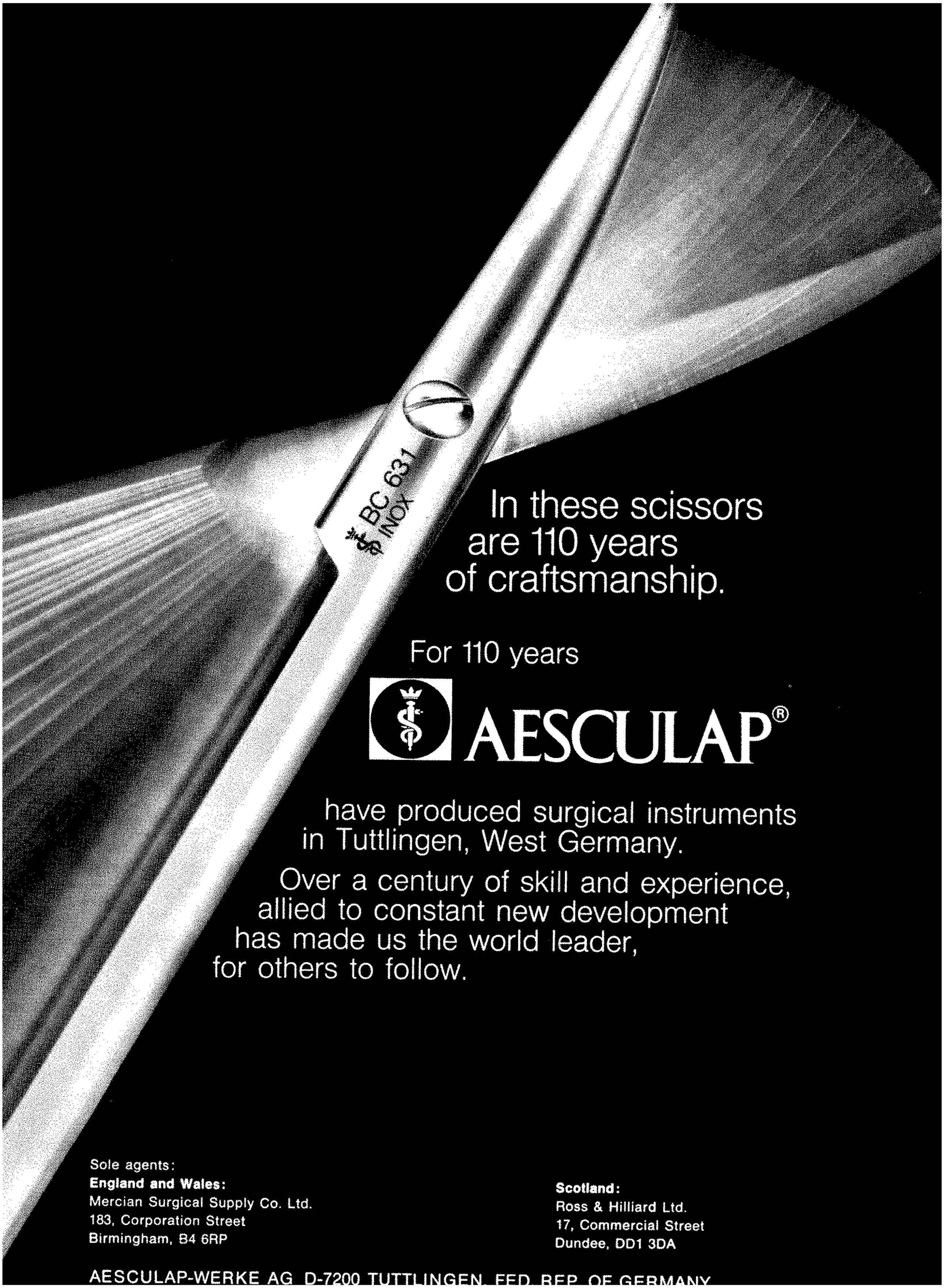

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KAPLAN M. H., COTLAR A. M. and STAGG S. J. (1964) Acute pancreatitis: six-year survey with evaluation of steroid therapy. *Am. J. Surg.* **108**, 24–30.

KUNE G. A. (1968) The challenge of severe acute pancreatitis. *Med. J. Aust.* **2**, 8–12.

LOUW J. H., MARKS I. N. and BANKS S. (1967) The management of severe acute pancreatitis. *Postgrad. Med. J.* **43**, 31–44.

MARKS I. N. and BANKS S. (1963) The etiology, clinical features and diagnosis of pancreatitis in South Western Cape. *S. Afr. Med. J.* **37**, 1039–1056.

MAYDAY G. B. and PHEILS M. T. (1970) Pancreatitis: a clinical review. *Med. J. Aust.* **1**, 1142–1144.

NUGENT F. W. and ZUBERI S. (1968) Treatment of acute pancreatitis. *Surg. Clin. North Am.* **48**, 595–599.

OLSEN H. (1974) Pancreatitis: a prospective clinical evaluation of 100 cases and review of the literature. *Am. J. Dig. Dis.* **19**, 1077–1090.

ONG G. B. (1968) Recurrent pyogenic cholangitis. In: SCOTT R. B. and WALKER R. M. (ed.) *Medical Annual*, 86th issue. Bristol, Wright, pp. 25–36.

SALZMAN E. W. and BARTLETT M. K. (1963) Pancreatic duct exploration in selected cases of acute pancreatitis. *Ann. Surg.* **158**, 859–863.

TRAPNELL J. E. (1966) The natural history and prognosis of acute pancreatitis. *Ann. R. Coll. Surg. Engl.* **38**, 265–287.

TRAPNELL J. E. (1972) The natural history and management of acute pancreatitis. *Clin. Gastroenterol.* **1**, 147–166.

TRAPNELL J. E. (1974) Acute pancreatitis in Great Britain—a review. *Med. J. Aust.* **2**, 450–455.

TRAPNELL J. E. and ANDERSON M. C. (1967) Role of early laparotomy in acute pancreatitis. *Ann. Surg.* **165**, 49–55.

TRAPNELL J. E., RIGBY C. C., TALBOT C. H. et al. (1974) A controlled trial of Trasylol in the treatment of acute pancreatitis. *Br. J. Surg.* **61**, 177–182.

WATTS G. T. (1963) Total pancreatectomy for fulminant pancreatitis. *Lancet* **2**, 384.

ZIMBERG Y. H. (1968) Pancreatitis: principles of management. *Surg. Clin. North Am.* **48**, 889–905.

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Statistics in *The British Journal of Surgery*

It is part of the clinical scientist's stock-in-trade to use statistical methods. In many instances, and by most readers, these can be taken on trust, but in that there is a wide variety of tests and, on occasion, disagreement amongst both amateurs and professionals on the best choice, it is always wise that authors quote the method used. It is indeed journal policy to quote methods, the reason for their choice and, in the case of clinical trials, the confidence or tolerance limits of the observed results. Delay in acceptance may occur if contributors do not include these details.

Br. J. Surg. Vol. 66 (1979) 404–405

Haemorrhagic cholecystitis

V. R. SHAH AND J. F. CLEGG*

SUMMARY

Two cases of haemobilia due to haemorrhagic cholecystitis are presented; only 28 other cases have been described. As there are so many more dramatic causes and treatment for haemobilia it is important for the surgeon to recognize that a common operation will suffice for this rare condition. In both cases bacteria were grown from the bile and it is to be hoped that bile culture will be recorded more commonly in future in cases of this interesting condition.

GASTROINTESTINAL haemorrhage is a very common emergency, but rarely is bleeding found to originate from the biliary tract (Manfredi, 1958). The most common causes of haemobilia these days are hepatic trauma and tumour of the liver and bile ducts. Sandblom (1972), via the world literature of haemobilia, found that the inflammatory causes of haemobilia accounted for only 13 per cent of cases and gallstones were implicated in 14·9 per cent of the series. Inflammatory causes include ascariasis (Ch'en Shu Chen, 1963), tuberculosis (Agrawal, 1967), hydatid disease (Goulston, 1955), sclerosing cholangitis (Larmi, 1966) and hepatic abscess (Urschel, 1963). Haemorrhagic cholecystitis, whether associated with gallstones or not, is a rare cause of haemobilia and gastrointestinal haemorrhage.

To date, 28 cases of haemorrhagic cholecystitis have been recorded in the world literature. In this paper we discuss the details of 2 further cases.

Case reports

Case 1: This man, a German electrical engineer, was admitted as an emergency on 12 May 1977 with a history of colicky upper abdominal pain for 1 day. The pain was severe and radiated to the front of his chest, causing him some difficulty in breathing. He gave a previous history of fatty food intolerance and his urine was noted to be dark. There was no previous history of jaundice.

Previously he had had an episode of probable biliary colic in 1973 and he had also had a splenectomy for traumatic rupture of the spleen in 1950.

On examination he was in severe pain. He had a pyrexia of 38·5 °C; the pulse rate was 72/min and regular. The blood pressure was 140/90 mmHg. In the abdomen there was tenderness and guarding in the right hypochondrium.

Investigations revealed the urine to contain bile. Other findings were: haemoglobin 15·9 g/dl; white cell count 9×10^9/l; bilirubin 126 μmol/l; alkaline phosphatase 17 KA units; prothrombin time 14 s; serum amylase 100 Somagyi units; aspartate transaminase 188 i.u.; faecal occult blood positive. Ultrasonic scan of the liver revealed distension of the intrahepatic and extrahepatic bile ducts including the gallbladder suggestive of an obstruction of the common bile duct.

Following admission, the patient developed deepening jaundice together with further attacks of biliary colic and pyrexia. Despite the absence of rigors he was thought to have cholangitis and on the day before operation he developed frank melaena.

At operation on 17 May 1977 gastroendoscopy was performed. This revealed no abnormality in the oesophagus, stomach or duodenum. A cholecystectomy and exploration of the common bile duct was performed.

The gallbladder was grossly distended and adherent to the liver and omentum. The wall was thick and inflamed and full of blood but no gallstones were present. Bleeding was arising from the inflamed epithelial lining of the gallbladder. The common bile duct was normal in size and contained clear bile. No abnormality could be found in the porta hepatis and an operative cholangiogram via the cystic duct was normal.

Histology of the gallbladder revealed evidence of mucosal and submucosal haemorrhage. In the external fat there was young fibrous tissue with some oedema. Bile from the gallbladder grew *Enterobactericae sporogenes.*

Following the operation the patient made a very satisfactory recovery and was discharged home. He has remained well during the subsequent year.

Case 2: This 58-year-old lady was admitted on 18 August 1972 with a 1-week history of pain in the epigastrium and right hypochondrium associated with vomiting. She had previously had six similar attacks over the previous 5 years. There was no history of jaundice but she had had fatty food intolerance.

On examination she was pyrexial (38 °C); her pulse rate was 100/min and blood pressure 160/100 mmHg. Abdominal examination revealed tenderness and guarding in the right hypochondrium. No mass was palpable.

Investigations carried out on admission revealed a serum bilirubin of 19 μmol/l, serum alkaline phosphatase of 18 KA units and serum albumin of 41 g/l. Serum globulin was 2·9 g/l and SGOT was 40 i.u. Double-dose cholecystography failed to visualize the gallbladder. Haemoglobin was 12·5 g/dl, white cell count 13×10^9/l, serum amylase 150 Somagyi units and prothrombin time 15 s.

A diagnosis of cholecystitis was made and arrangements were made for operation. However, 6 hours before operation the patient had a frank haematemesis and passed a melaena stool. At laparotomy a grossly inflamed gallbladder was found to be stuck to surrounding structures. The gallbladder was full of blood and contained stones. The common bile duct was dilated and contained blood clot, as did the stomach and duodenum.

A cholecystectomy and exploration of the common bile duct was performed together with liver biopsy. Bile culture grew pneumococci.

Following operation the patient made a good recovery and a subsequent T tube cholangiogram was within normal limits. There were no further episodes of haematemesis and melaena and the patient is well 5 years later.

Discussion

Most upper gastrointestinal bleeding arises in the oesophagus, stomach or duodenum. When a diagnostic study of this region is negative, it is well to keep in mind the possibility of haemobilia. If haemorrhage occurs in the gallbladder, several possibilities may arise. First, the blood may clot in the gallbladder, in which case the gallbladder will enlarge. Secondly, the blood may pass into the common bile duct and then into the duodenum causing either haematemesis or melaena. If the blood clots in the bile ducts, obstructive jaundice may occur with attacks of biliary colic. In certain cases of haemorrhagic cholecystitis the enlarged gallbladder has ruptured into the peritoneal cavity (Polse et al., 1976). It is surprising that haemorrhagic cholecystitis is so rare, as Gad (1962) examined a large series of patients with cholelithiasis and found 25 per cent of them to have a positive faecal occult blood.

Quincke (1871) described a diagnostic triad for haemobilia consisting of biliary colic, gastrointestinal haemorrhage and jaundice. Unfortunately, if the cause of the haemobilia is haemorrhagic cholecystitis, this useful triad is often overlooked, as in our 2 cases, because the patient initially presents with acute cholecystitis and the gastrointestinal haemorrhage comes as a secondary phenomenon. In our 2 cases, both patients were thought to have stress ulceration, and indeed in our second case the patient had a gastroduodenal endoscopy for this specific reason; no source for the bleeding was found. Nevertheless, it might have shown blood issuing from the ampulla of Vater and this investigation is always worthwhile in any case of gastrointestinal haemorrhage.

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If haemobilia is considered a possible diagnosis for gastrointestinal bleeding, the correct preoperative investigation is selective hepatic artery angiography, as this may accurately localize the source of the bleeding and exclude the more common causes of haemobilia such as hepatic artery aneurysms or hepatic tumour. Unfortunately, this particular investigation has never been performed in any reported case of haemorrhagic cholecystitis and was not carried out in our 2 patients, the reason being that the diagnosis was not made preoperatively. Fortunately, in haemorrhagic cholecystitis the diagnosis is obvious at operation on opening the gallbladder and cholecystectomy will cure the condition. In our cases the common bile duct was explored and this seems to be a wise manoeuvre, as in *Case* 2 the common bile duct was obstructed by the presence of blood clots and, of course, these could be removed during the course of exploration. In the first case the common bile duct was explored despite a normal cholangiogram to make absolutely certain that there was no small bleeding point within the common bile duct.

In the case associated with gallstones pneumococci were isolated from bile culture. This is an unusual organism to be present in bile, as bile acids are bactericidal to the pneumococcus. However, if the concentration of the bile salts is high, as in the concentrated bile in the gallbladder, then this bactericidal property is lost due to aggregation of bile salt molecules and the organism can survive. The presence of this organism with the gallstones was possibly an important cause of the haemorrhagic ulceration of the gallbladder mucosa, as in the lung it can cause a haemorrhagic form of inflammation. Nevertheless, this particular organism has not been associated with the other cases of haemorrhagic cholecystitis in the world literature; unfortunately, bile culture has only been recorded on very few occasions previously. The other case which was not associated with the presence of gallstones in the gallbladder had *Enterobactericae sporogenes* cultured from the bile. This is a much more common organism in the biliary tree and probably infects the gallbladder in an ascending manner, whereas the mode of infection with the pneumococcus is probably haematogenous.

References

AGRAWAL H. S., BENSON J. W. and MAJOR J. J. (1967) An unusual case of haemobilia. *Arch. Surg.* **95**, 202–206

CH'EN SHU-CHEN, SHEN K'UEI, HO SAN-KUANG et al. (1963) On the aetiology, pathogenesis, diagnosis and treatment of masssive haemorrhage from the intrahepatic bile duct. *VIII National Congress of Surgery Abstracts* (Peking), p. 28.

GAD P. (1962) Occult bleeding in gall stone disorders. *Nord. Med.* **68**, 1069–1071.

GOULSTON E. (1955) Massive haemobilia from an hydatid cyst of liver. *Aust. NZ J. Surg.* **25**, 302–303.

LARMI T. K. (1966) Hemobilia associated with cholecystitis, post-cholecystectomy condition, and trauma. *Ann. Surg.* **163**, 373–381.

MANFREDI D. H. (1958) Gastrointestinal hemorrhage in the biliary tract. *N Y J. Med.* **58**, 2397–2401.

POLSE S., STONEY R. J. and BALDWIN J. N. (1967) Hemorrhage of the gallbladder. *Calif. J. Med.* **107**, 51–53.

QUINCKE H. (1871) Ein Fall von Aneurysm der Leberarterie. *Berl. Klin. Wochenschr.* **8**, 349–352.

SANDBLOM P. (1972) *Hemobilia.* Springfield, Ill., Thomas. p. 6.

URSCHEL H. C. JUN., SKINNER D. B. and MCDERMOTT W. V. (1963) Hemobilia secondary to liver abscess. *JAMA* **186**, 797–799.

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Br. J. Surg. Vol. 66 (1979) 406

Primary hydatid cyst of the gallbladder

A. M. RIGAS, G. M. KARATZAS, N. C. MARKIDIS, D. S. BONIKOS, G. G. SOTIROPOULOU AND G. SKALKEAS*

SUMMARY

An unusual case of hydatid cyst of the gallbladder is presented. The difficulties in diagnosis are discussed. There is no other report of such a cyst in the world literature.

HYDATID disease is common in Greece. In a population of 10 000 000, approximately 500 patients are operated upon every year. Occasionally the disease is difficult to diagnose before operation. One such case is presented.

Case report

A 65-year-old woman was admitted in April 1978 with a history of intermittent pain in the right hypochondrium, radiating to the back, and vomiting. There was no anaemia, cyanosis, jaundice, oedema, ascites or lymphadenopathy. The liver and spleen were not felt. On investigation the haemoglobin was 13 g/dl, the blood urea was 6·6 mol/l and the liver function tests were normal.

Barium meal and barium enema examinations and chest X-rays were normal. A cholangiogram revealed a common bile duct of normal calibre without stones; the gallbladder shape was abnormal with a filling defect (*Fig.* 1). The liver scan was within normal limits. A presumptive diagnosis of gallstones or a gallbladder anomaly was made.

Exploratory laparotomy revealed a cyst of the body of the gallbladder and cholocystectomy (including the cyst) was performed. There was no other hydatid cyst detected in the abdomen. The patient was discharged on the ninth postoperative day and has remained well since.

The gallbladder specimen measured 8×4 cm in its greatest dimensions and it had a thick wall. There was an ovoid thin-walled cyst measuring 5×4 cm loosely attached to the external surface of the body of the gallbladder. The cyst contained numerous thin, white, soft concentric membranes (*Fig.* 2). The appearance suggested a diagnosis of an echinococcal cyst, which was confirmed on microscopic examination. There was no significant histopathological abnormality of the gallbladder, which did not communicate with the cyst.

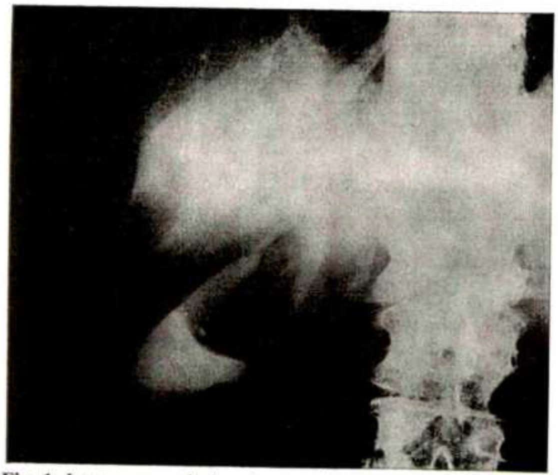

Fig. 1. Intravenous cholangiogram showing a common bile duct of normal calibre but the gallbladder has an abnormal shape.

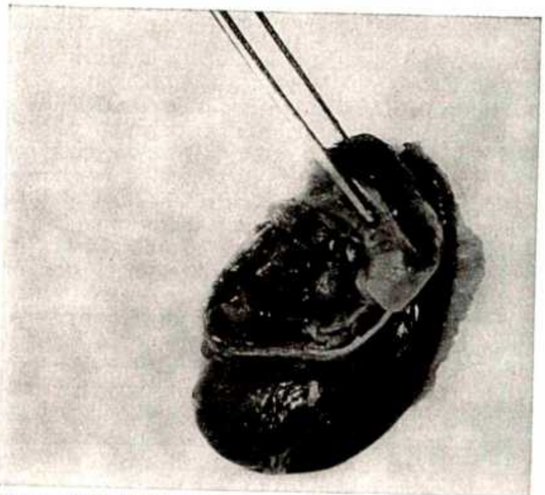

Fig. 2. Opened hydatid cyst: note the membranes arranged in a concentric laminated fashion.

Discussion

The most frequent site of hydatid disease is the liver because it is the first filter of parasitic embryos migrating from the intestine. The incidence of disease at this site varies from 60·3 per cent (Kourias, 1974) to 93 per cent (Emamy and Asadian, 1976; Jones, 1978).

A review of more than 14 000 cases of hydatid disease in Greece did not include any case of hydatid cyst of the gallbladder (Prokos et al., 1964). No other report of such a cyst has been found in the world literature. It is usually only large cysts that produce symptoms. In our case the size of the cyst was small (5×4 cm approximately) and the symptoms suggested possible gallstones because of some derangement of function of the gallbladder.

The probable mode of spread of the parasitic embryo to the gallbladder was from the gut via the lymphatics. In our case total excision of the cyst, the ideal procedure for any hydatid cyst, was feasible because it was attached to the gallbladder wall.

References

EMAMY D. M. H. and ASADIAN A. (1976) Unusual presentation of hydatid disease. *Am. Surg.* **42**, 875–878.

JONES C. T. (1978) Cestodes. In: *Intestinal Parasites: Clinics in Gastroenterology*. Philadelphia, Saunders, pp. 121–125.

KOURIAS G. B. (1974) Hydatid disease of the liver and other viscera. In: MAINGOT R. (ed.) *Abdominal Operations*, 6th ed. New York, Appleton–Century–Crofts, pp. 1048–1061.

PROKOS G., SFIKAKIS P. and DORDOFIKIS N. (1964) Hydatid disease in Greece. *Acta Chir. Hell.* **2**, 79.

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Splenic cysts: a review of 6 cases

W. G. HUMPHREYS AND G. W. JOHNSTON*

SUMMARY

Benign cysts of the spleen are rare. Six cases have been managed in this hospital in the past 25 years. The history, physical findings and investigations are reviewed. It is suggested that splenectomy is the treatment of choice as it carries a low morbidity and mortality.

WITH the increasing incidence of road traffic and sporting accidents, the spleen has become the most frequently injured intra-abdominal organ in cases of closed trauma. There is little argument that immediate splenectomy is the treatment of choice for the acutely ruptured spleen, since delayed diagnosis and the surgery of delayed rupture have a high morbidity and significant mortality (Zabinski and Harkins, 1943). Douville and Bélanger (1972) reported that delayed rupture of the spleen may occur in up to 14 per cent of all cases of splenic injury, but the development of a splenic pseudocyst is a rare late complication of splenic trauma (Halvorsen et al., 1974).

This report was prompted by the recent management of 4 such cases in one surgical unit. Review of the hospital records produced only 2 further cases in the previous 25 years, and all 6 are reported here.

Case reports

Case 1: A 16-year-old male was thrown from his motorcycle and sustained an injury to his left upper abdomen, but he did not require hospitalization. One year later, he presented with a dull ache in his left hypochondrium and a mass in the left upper abdomen was obvious on inspection and palpation. The clinical and ulrasonographic diagnosis was traumatic pancreatic pseudocyst, but at laparotomy a large splenic cyst was found. After splenectomy there was an uneventful recovery with alleviation of the patient's symptoms.

Case 2: A 41-year old male who was involved in a road traffic accident sustained blunt trauma to the abdomen and was admitted with left-sided upper abdominal pain and haematuria. A palpable mass in the left hypochondrium and left loin was thought to be a perirenal haematoma. Intravenous urography confirmed a small left renal capsular rupture. On conservative management the pain and haematuria resolved but a cystic mass persisted in the abdomen. Renal arteriography showed normal renal vasculature, but selective coeliac angiography demonstrated the presence of a splenic cyst. As yet, this patient has not had surgical intervention.

Case 3: A 24-year-old female presented with a history of abdominal swelling for 1 year and left hypochondrial pain for 4 months. There was no relevant past history and the only positive physical finding was splenomegaly. A preoperative diagnosis of splenic cyst was made from the liver scan, ultrasonography and renal tomography. At laparotomy a unilocular splenic cyst 18 cm in diameter and 1600 g in weight was removed. The patient's postoperative course was uncomplicated.

Case 4: A 58-year-old female was admitted with a 1-month history of anaemia, weakness and vague upper abdominal pain. Examination revealed a mass in the left hypochondrium which was shown by scintiscan, barium meal examination and ultrasonography to be of splenic origin. It was noted that at 12 years of age she had fallen from her bicycle and had sustained fractured ribs on the left side. At operation a cyst 25 cm in diameter was removed with splenectomy The patient's operative course was satisfactory and her anaemia improved. Histologically, this was a simple cyst, probably of traumatic origin.

Case 5: A 16-year-old girl was readmitted 4 months after appendicectomy with a history of left shoulder-tip pain and a mass in the left hypochondrium. Barium meal examination and pyelography demonstrated splenic enlargement and a splenic portogram showed a cyst of the spleen 18 cm in diameter. The diagnosis was confirmed at surgery when a 1500-g mass was removed. Histology showed a simple unilocular cyst and normal splenic tissue. The girl remains well.

Case 6: A 50-year-old man was referred with a short history of pain in the left hypochondrium. In the past he had sustained blunt upper abdominal trauma. On plain X-ray of the abdomen a calcified lesion was noted in the left hypochondrium. This was shown to be extrarenal on pyelography and to be cystic on ultrasonography. It was thought to be an adrenal cyst, but at laparotomy a calcified splenic cyst 5 cm in diameter and 180 g in weight was removed by splenectomy. The patient's subsequent progress was satisfactory.

Discussion

Splenic cysts are rare and it is unusual for a physician or surgeon to see many such cases in his clinical practice (Topilow and Steinhoff, 1975). The cysts probably arise as the result of organization and liquefaction of a subcapsular haematoma of the spleen.

Since the original description of this lesion by Andral in 1829, fewer than 600 cases of non-parasitic benign splenic cyst have been reported in the world literature (Robbins et al., 1978), mainly in three large collected series (Fowler, 1953; Posener and Litherland, 1956; Qureshi et al., 1964). According to Qureshi and Hafner (1965), accurate preoperative diagnosis has been rare, but a high index of suspicion allied to careful investigation should reverse this unsatisfactory situation.

All patients in this series had a classic history of left hypochondrial pain with a palpable mass. In two-thirds of the cases there was a history of past trauma. Symptoms were present for a mean period of 18½ months before investigation and this delay is typical of that reported by others (Grosdidier et al., 1974). The density of the lesion may be demonstrated by ultrasonography or CAT scan and the position of the mass relative to the left kidney can be demonstrated by pyelography and selective angiography. Splenectomy is indicated to alleviate pain, remove the mass and obviate the risks of infection or late rupture. In the 5 patients submitted to laparotomy and splenectomy, the splenic lesions were histologically simple cysts with a mean diameter of 15·9 cm (range 5·5–20 cm) and a mean weight (combined with the spleen) of 1375 g (range 180–3000 g). The outcome was favourable in all cases and the sixth patient is asymptomatic but remains under review.

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References

DOUVILLE E. L. and BÉLANGER R. (1972) Delayed rupture of the spleen. *Int. Surg.* **57**, 880–882.

FOWLER R. H. (1953) Collective review of non-parasitic benign cystic tumours of the spleen. *Int. Abstr. Surg.* In: *Surg. Gynecol. Obstet.* **96**, 209–227.

GROSDIDIER J., BOILEAU F. and RICHAUME B. (1974) Pseudokystes hémorragiques post-traumatiques de la rate. *Sem. Hôp. Paris* **50**, 2556–2559.

HALVORSEN J. F., SEMB B. K. H. and MARSETH K. (1974) Post-traumatic pseudocyst of the spleen with hypersplenism. *Acta Chir. Scand.* **140**, 571–575.

POSENER L. J. and LITHERLAND O. K. (1956) An epidermoid cyst of the spleen. *Can. Med. Assoc. J.* **75**, 510–512.

QURESHI M. A. and HAFNER C. D. (1965) Clinical manifestations of splenic cysts: study of 75 cases. *Am. Surg.* **31**, 605–608.

QURESHI M. A., HAFNER C. D. and DORCHAK J. R. (1964) Non-parasitic cysts of the spleen: report of 14 cases. *Arch. Surg.* **89**, 570–574.

ROBBINS F. G., YELLIN A. E., LINGVA R. W. et al. (1978) Splenic epidermoid cysts. *Ann. Surg.* **187**, 231–235.

TOPILOW A. A. and STEINHOFF N. G. (1975) Splenic pseudocyst: a late complication of trauma. *J. Trauma* **15**, 260–263.

ZABINSKI E. J. and HARKINS H. N. (1943) Delayed splenic rupture: a clinical syndrome following trauma. *Arch. Surg.* **46**, 186–213.

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The Royal College of Surgeons of Edinburgh: Endowment Fund Appeal

The Royal College of Surgeons of Edinburgh has launched a world-wide, public appeal to set up an endowment fund. In explaining the purpose of this appeal the President, Professor Andrew Wilkinson, writes:

> In the past, the financial independence of the College and the services which it provides have depended on the subscriptions paid by its Fellows and from investments. There has never been an endowment fund and the College has never in its 473 years appealed for money.
>
> If the College is to continue as a leading centre of surgical education however, it is essential that its teaching programmes and related activities are not curtailed through lack of space. At present the financial state of the College is good but, to achieve its aims and to ensure its financial stability and development, an endowment fund of £1·5 m is needed.

Some of the money which it is hoped will be raised will be used to provide living accommodation for surgeons in training and for surgeons visiting Edinburgh for further study and experience. It is also intended to provide extra space for the library, and rooms for examinations and scientific meetings. Nearly £600 000 has already been contributed, largely by support from the College's Fellows and Licentiates in 92 countries, and the Council has now decided to broaden the scope of the appeal.

In a special appeal message, HRH The Prince Philip, Duke of Edinburgh, who is Patron and an Honorary Fellow of the College, writes:

> During the four hundred and seventy-three years since King James IV granted a Royal Charter, the Royal College of Surgeons of Edinburgh has set and enforced the most stringent conditions for those wishing to qualify as surgeons and it has succeeded in maintaining the highest standards of professional conduct among its Fellows. Today, three-quarters of its ten thousand Fellows are practising outside the British Isles and in every continent of the world.
>
> The long experience and traditions of the Royal College are so highly valued that young men and women from overseas are pressing to come to Edinburgh to study their craft, and the services they will be able to render their own people when they get home is a measure of the contribution the Royal College of Surgeons of Edinburgh is making to the welfare of mankind.

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H_2-antagonists in the treatment of recurrent ulceration after vagotomy

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SUMMARY

Twenty-two patients with recurrent ulceration following vagotomy with and without a drainage procedure have been treated with histamine H_2-antagonists and followed for up to 3 years. Four of a group of 6 patients responded to a single therapeutic course. Ten of 16 patients assigned to long term maintenance treatment remain symptom-free. Cimetidine may be an alternative to further surgery in the treatment of some patients with recurrent ulceration after vagotomy.

CIMETIDINE is an effective drug in the treatment of duodenal ulceration (Winship, 1978). The symptomatic (Haggie et al., 1976) and endoscopic (Wyllie, 1978) relapse rate is high when active treatment is discontinued, and it has become clear that once the ulcer has healed, maintenance therapy is required to prevent recurrence. How long maintenance treatment can be given is at present a matter of conjecture, but observations in patients treated in this way for up to 1 year appear to show considerable therapeutic success (Bodemar and Walan, 1978; Gudmand-Hoyer et al., 1978).

Recurrent ulceration after vagotomy for duodenal ulceration, with or without a drainage procedure, is not uncommon (Goligher et al., 1978). It is often regarded as more resistant to medical management than the original ulcer (Balint et al., 1957). The only effective treatment is further surgery, which many patients are reluctant to accept if some suitable alternative is available. Observations have been made on the value and limitations of H_2-antagonists in the treatment of patients with recurrent ulceration after vagotomy.

Patients and methods

Twenty-two patients with recurrent ulceration after vagotomy have been treated over a period of 3 years. Their ages ranged from 25 to 67 years, and there were 2 female patients. In all cases the original ulcer was in the duodenum. In 14 patients the operation performed was proximal gastric vagotomy (highly selective vagotomy) and in the remainder, vagotomy and pyloroplasty (4 truncal, 4 selective vagotomy). In 21 patients the diagnosis of recurrent ulceration was confirmed on endoscopy, one ulcer being situated in the prepyloric region and the remainder in the duodenum. In one patient endoscopy was contraindicated because of pre-senile dementia, but the recurrence (after proximal gastric vagotomy) was confirmed by barium meal examination. In all patients plasma gastrin estimations were made to exclude the Zollinger–Ellison syndrome.

Three patients were treated with metiamide until the drug was withdrawn from use, and the remainder were treated with cimetidine. The first 6 patients were treated with a dose of 200 mg three times daily and 400 mg at night for periods of 6–8 weeks, the aim being to achieve an asymptomatic state for 4 weeks. Thereafter no further treatment was given. By this time we had come to appreciate the limitations of a single therapeutic course of cimetidine in the treatment of duodenal ulceration and the need for some form of maintenance therapy. All subsequent patients were therefore treated with an initial therapeutic regimen of 1 g/day for 6 weeks followed by maintenance dosage of 400 mg at night. In one patient treatment was inadvertently given for 8 weeks, and in another patient treatment was extended for a further 6 weeks without success.

Only 12 patients had repeated endoscopy as part of their assessment, the investigation being accepted as necessary by those with persistent or recurrent symptoms, but generally refused by patients who were asymptomatic. Many of these patients had previously been involved with clinical trials of H_2-antagonists with repeated endoscopy for assessment, hence the difficulty in persuading asymptomatic patients into further endoscopy.

Results

Tables I and II summarize the results, the groups of patients being determined by the type of treatment and the outcome. There were 6 patients (*Table I*) treated at the beginning of the study with a single treatment regimen of 1·0 g of either metiamide or cimetidine for 6–8 weeks, excepting one patient whose treatment was continued for 16 weeks. The duration of treatment was determined by the time taken to control symptoms, but none of these patients was given maintenance treatment. Four patients have remained asymptomatic for 1–2½ years, though none of them has had further endoscopy. In 2 of the asymptomatic patients the recurrent ulcer may have been induced by ingestion of aspirin or phenylbutazone. Two patients in this group developed symptomatic recurrence at 1 and 2 years respectively, and both showed recurrent duodenal ulcers on endoscopy. Both patients have subsequently responded symptomatically to further treatment with cimetidine, including maintenance treatment.

There were 16 patients with recurrent ulceration for whom the proposed treatment was cimetidine 1·0 g/day for 6 weeks, followed by maintenance therapy of 400 mg at night. *Table II* shows that 10 patients remain symptom-free on this regimen for periods of 9–21 months, and in 8 endoscopy has confirmed healing. One patient relapsed on inadvertently stopping treatment but responded to further cimetidine. There were 6 treatment failures, 3 of these were recurrences in patients on maintenance treatment and 2 of these have subsequently been treated by operation. In 2 patients the ulcers failed to heal on the treatment regimen and these patients were treated by partial gastrectomy. The remaining patient responded symptomatically to cimetidine but on the fourth week of treatment was admitted with a massive haemorrhage and treated by emergency partial gastrectomy.

Discussion

These observations attempt to assess the potential value of H_2-antagonists in the treatment of recurrent ulceration after vagotomy. The aetiology of the recurrence has not always been investigated, and only a

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Table I: THE RESULTS OF TREATMENT WITH A COURSE OF H_2-ANTAGONISTS WITHOUT MAINTENANCE THERAPY

Case no.	Age (yr)	Sex	Operation	Years to recurrence	Treatment and result	Follow-up
1	54	M	SV+P	7	Metiamide 6 wk: no further symptoms	2¼ yr
2	67	M	PGV	2	Metiamide 8 wk: no further symptoms	2 yr
3	52	M	PGV	5	Metiamide 6 wk: no further symptoms	1¼ yr
4	37	M	PGV	0·5	Cimetidine 6 wk: no further symptoms	1 yr
5	52	M	PGV	2·5	Cimetidine 16 wk: further recurrence	1 yr
6	50	F	TV+P	0·5	Cimetidine 8 wk: further recurrence	2 yr

Cases 2 and 3 may have been induced by aspirin and phenylbutazone respectively.
PGV, Proximal gastric vagotomy; SV+P, selective vagotomy and pyloroplasty; TV+P, truncal vagotomy and pyloroplasty.

Table II: THE RESULTS OF TREATMENT WITH A COURSE OF H_2-ANTAGONISTS WITH MAINTENANCE THERAPY

Case no.	Age (yr)	Sex	Operation	Years to recurrence	Treatment and result	Follow-up
7	50	M	TV+P	5	Cimetidine for 6 wk and maintenance: symptom-free	21 mth
8	59	M	PGV	4	Cimetidine for 6 wk and maintenance: symptom-free	21 mth
9	63	M	PGV	1·5	Cimetidine for 6 wk and maintenance: symptom-free	15 mth
10	26	M	PGV	0·5	Cimetidine for 6 wk and maintenance: symptom-free	15 mth
11	56	M	PGV	4·5	Cimetidine for 6 wk and maintenance: symptom-free	15 mth
12	52	M	SV+P	2	Cimetidine for 6 wk and maintenance: symptom-free	12 mth
13	34	M	PGV	6	Cimetidine for 6 wk and maintenance: symptom-free	12 mth
14	66	M	TV+P	0·25	Cimetidine for 6 wk and maintenance: symptom-free	9 mth
15	35	M	PGV	0·5	Cimetidine for 6 wk and maintenance: symptom-free	9 mth
16	44	F	PGV	1·5	Had relapsed on stopping maintenance but responded to further treatment	15 mth
17	62	M	PGV	2	Cimetidine for 8 wk: responded but recurred on maintenance after 4 wk; Polya gastrectomy	
18	40	M	TV+P	5	Cimetidine for 4 wk: responded but recurred on maintenance after 6 wk; Billroth I gastrectomy	
19	25	M	PGV	0·5	Three 6-wk courses of cimetidine with good response but recurs on maintenance treatment: operation advised	
20	36	M	SV+P	5	Cimetidine for 6 wk: failed to respond; Polya gastrectomy	
21	35	M	SV+P	0·5	Cimetidine for 12 wk: failed to respond; Polya gastrectomy	
22	30	M	PGV	3	Cimetidine for 4 wk: symptomatic response but admitted with massive bleed; emergency Polya gastrectomy	

PGV, Proximal gastric vagotomy; SV+P, selective vagotomy and pyloroplasty; TV+P, truncal vagotomy and pyloroplasty.

limited number of secretion studies have so far been performed. It may well be that the cause of recurrent ulceration differs with proximal gastric vagotomy compared with vagotomy and pyloroplasty. The basal fasting serum gastrin levels were all less than 120 pg/ml, and although no calcium- or secretin-stimulation tests were performed, it seems unlikely that any of the patients suffered from the Zollinger–Ellison syndrome, although this cannot absolutely be excluded (Deveney et al., 1977). Nevertheless, in the treatment of a patient with recurrent ulceration after any type of vagotomy, the choice lies between further surgery or drug therapy. Hitherto, treatment with drugs has generally been unsatisfactory and not without risk (Everson and Allen, 1954; Beal, 1959). Stabile and Passaro (1976), in a detailed review, calculated a mortality of 10·8 per cent and a relapse rate of 42·1 per cent in patients on medical treatment.

The diagnosis of recurrent ulceration was made by barium meal examination in one patient and by endoscopy in the remainder. The response to treatment has been judged on the basis of symptoms. In all patients who failed to respond to treatment or who subsequently relapsed, ulceration has been confirmed by endoscopy or at operation. It is recognized that ulcers may persist in a few asymptomatic patients (Burland et al., 1978) and this occurred in the patient admitted with haemorrhage. Therefore, the number of asymptomatic patients overestimates the number of healed ulcers.

In *Table I* 4 of the 6 patients responded to a single therapeutic course of cimetidine, an unusual event in the light of subsequent experience. A partial explanation may be that the ulcer may have been drug-induced (aspirin, phenylbutazone) and withdrawal of the drug may have been more beneficial than treatment with cimetidine.

Of the 16 patients who were entered into a therapeutic uncontrolled trial of cimetidine with maintenance treatment, 10 (62·5 per cent) have continued symptom-free for periods of 9–21 months. Delle Fave et al. (1977) noted that 9 of his 10 patients with recurrent ulceration following gastrectomy had healed within 2 months. Hoare et al. (1978) found in 17 of their 20 patients that the ulcer had healed at 6 weeks and Wastell et al. (1978) found that 4 of their 8 patients with recurrence after proximal gastric vagotomy had healed at 6 weeks. Saunders et al. (1978) have treated 13 patients with recurrent ulceration after surgery with full dosage (1 g/day) of cimetidine for 1 year, and of these, 10 healed within 1 month, 2 within 3 months and the other patients only after increasing the dosage to 1·6 g/day. Three recurrences were found during treatment (23 per cent), and after stopping treatment 3 patients remained well for more than 7 months.

Although Kennedy and Spencer (1978), in a controlled clinical trial in 12 patients using cimetidine versus placebo, found no significant difference in the rate of healing at 6 weeks, the present evidence indicates a therapeutic role of H_2-antagonists in the treatment of recurrent ulceration after gastric surgery. The majority of recurrent ulcers heal with a therapeutic course of 6 weeks' duration, though in some patients increased dosage or more prolonged treatment may be required. Cessation of treatment is not necessarily followed by relapse, but maintenance therapy is almost certainly desirable. The question which cannot yet be answered is: 'How long should treatment be continued?' It has been suggested that cimetidine should not be prescribed for more than a year because of the unknown effects of long term treatment (Leading Article, 1978). In the treatment of chronic duodenal ulceration cessation of maintenance treatment is frequently followed by relapse, and there is no reason to suppose that there will be any difference with recurrent ulcer. In these circumstances the only justification for treating recurrent ulceration with H_2-antagonists may be to 'buy time'.

The surgical treatment of recurrent ulceration is often technically difficult, with an operative mortality considerably greater than that of the initial operation. There may, therefore, be justification for treating such patients with cimetidine for prolonged periods, provided that adequate supervision is maintained.

References

BALINT J. A., COOPER G. W., PRICE E. C. V. et al. (1957) The management of anastomotic ulcer. *Lancet* **2**, 551–555.

BEAL J. M. (1959) The surgical treatment of marginal ulcer. *Am. J. Surg.* **25**, 1–7.

BODEMAR G. and WALAN A. (1978) Maintenance treatment of recurrent peptic ulcer by cimetidine. *Lancet* **1**, 403–407.

BURLAND W. L., HAWKINS B. and HORTON R. J. (1978) Maintenance treatment of duodenal ulcer with cimetidine. *Br. Med. J.* **2**, 433.

DELLE FAVE G. F., PAOLUZI P., BERGONZI L. et al. (1977) Cimetidine and postgastrectomy recurrent ulcer. *Rendiconti Gastroenterol.* **9**, 150–151.

DEVENEY C. W., DEVENEY K. S., JAFFE B. M. et al. (1977) Use of calcium and secretin in the diagnosis of gastrinomas (Zollinger–Ellison syndrome). *Ann. Intern. Med.* **87**, 680–686.

EVERSON T. C. and ALLEN M. J. (1954) Gastrojejunal ulceration. *Arch. Surg.* **69**, 140–147.

GOLIGHER J. C., HILL G. L., KENNY T. E. et al. (1978) Proximal gastric vagotomy without drainage for duodenal ulcer: results after 5–8 years. *Br. J. Surg.* **65**, 145–148.

GUDMAND-HOYER E., BIRGER-JENSEN K., KRAG E. et al. (1978) Prophylactic effect of cimetidine in duodenal ulcer disease. *Br. Med. J.* **1**, 1095–1097.

HAGGIE S. J., CLARK C. G., BLACK J. W. et al. (1976) Clinical experience with metiamide. *Fed. Proc.* **35**, 1948–1952.

HOARE A. M., JONES E. L. and HAWKINS C. G. (1978) Cimetidine for ulcers recurring after gastric surgery. *Br. Med. J.* **1**, 1325–1326.

KENNEDY T. and SPENCER A. (1978) Cimetidine for recurrent ulcer after vagotomy or gastrectomy; a randomised controlled trial. *Br. Med. J.* **1**, 1242–1243.

LEADING ARTICLE (1978) *Br. Med. J.* **1**, 1435–1436.

SAUNDERS J. H. B., CARGILL J. M., PEDEN N. R. et al. (1978) Cimetidine for ulcer recurring after surgery. *Br. Med. J.* **1**, 1619.

STABILE B. E. and PASSARO E. JUN. (1976) Recurrent peptic ulcer. *Gastroenterology* **70**, 124–135.

WASTELL C., MCGREGGOR C. P. and HALE J. (1978) Treatment of recurrent ulcer after vagotomy with cimetidine. *Br. J. Surg.* **65**, 367 (Abstr.).

WINSHIP D. H. (1978) Cimetidine in the treatment of duodenal ulcer. Review and commentary. *Gastroenterology* **74**, 402–406.

WYLLIE J. H. (1978) Histamine H_2-receptor antagonist in treatment of peptic ulcer. *Postgrad. Med.* **63**, 91–96.

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The excretion of alkaline ribonuclease by children undergoing surgery

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SUMMARY

The excretion of alkaline ribonuclease has been measured in the urine of two groups of children after major operations. The excretion was significantly increased in all patients after open operations on the heart and in many of those who were operated on soon after birth for anomalies in the intestine. It is suggested that these elevations may indicate a disturbance of pancreatic function.

In adults severe pancreatitis has been observed after some kinds of cardiac operation. The condition has been attributed to the disturbance of the blood supply and is most common in patients who die (Feiner, 1976). Elevation of the concentrations of amylase in serum and of urine of up to ten times the normal level are taken as indications of pancreatitis and, following recovery, the amylase concentrations in both serum and urine rapidly return to within the normal range. Similar large increases in the serum amylase concentration may be observed during the first 2 days after operations on the chest and a moderate elevation may persist for several further days (Hennings and Jacobson, 1974).

It has been shown that three degrees of malnutrition in children can be recognized according to the concentrations of ribonuclease in the urine and serum (Sigulem et al., 1973). We have shown recently that the urinary output of ribonuclease may be greatly increased in children after injury by burning or scalding (Barlow and Whitear, 1977). We have, therefore, examined the urinary output of ribonuclease in two groups of children, one group having had open operations on the heart and the other, operative treatment soon after birth for various intestinal abnormalities.

Patients and methods

Urine was obtained from 6-hourly specimens collected postoperatively from 31 children for up to 16 days as part of a series of metabolic balance studies. The urine was collected into ion-free plastic bags (Hollister) and deep frozen without preservative until required for assay; urine can be stored frozen for up to 12 months without any effect on the enzyme activity. Control urine values were obtained from measurements in 13 children aged 10 months to 10 years who had been admitted to hospital for minor operations and from 3 normal neonates (21 occasions) and from 2 neonates with Beckwith's syndrome (4 occasions). Details of the patients, diagnoses and operations are shown in *Table I*.

The urinary alkaline ribonuclease activity was measured as described by Barlow and Whitear (1977).

Results

The output of ribonuclease in the 13 control children aged 10 months to 10 years was $0{\cdot}43 \pm 0{\cdot}29$ Kunitz units 24 h^{-1} kg^{-1} (mean ± s.d.), and in 25 single 24-h collections from neonates was $0{\cdot}52 \pm 0{\cdot}2$ Kunitz units 24 h^{-1} kg^{-1} (mean ± s.d.). The method had a coefficient of variation of 13·9 per cent.

After open heart operations excretion of ribonuclease in the urine was significantly raised for about 8 days and in some patients for even longer (*Table II*). The urinary excretion of ribonuclease, averaged over the period for which collections were made, was also increased in 14 out of 20 patients operated on soon after birth for intestinal anomalies. Even in 3 of those cases that did not show an overall increase there were several days when significantly high levels were observed. There was no correlation between urine volume and the excretion of the ribonuclease. Gaps in *Tables II* and *III* indicate that the ribonuclease activity was not measured on these days either because there were no urine collections made or because the collections were incomplete.

Table I: DETAILS OF THE CASE SERIES

Case no.	Age	Diagnosis and operation
1	4 mth	Ventricular septal defect; patent foramen ovale
2	4 d	Total anomalous pulmonary venous drainage
3	7 yr	Ventricular septal defect
4	23 d	Pulmonary stenosis
5	7 mth	Transposition of the great arteries; ventricular septal defect; patent ductus arterosis
6	6 mth	Transposition of the great arteries
7	9 mth	Transposition of the great arteries
8	5 mth	Transposition of the great arteries
9	14 d	Total anomalous pulmonary venous drainage; patent ductus arterosis; atrial septal defect
10	1 mth	Ventricular septal defect; aortic stenosis
11	14 d	Total anomalous pulmonary venous drainage
12	7 d	Oesophageal atresia and tracheo-oesophageal fistula
13	3 d	Oesophageal atresia and tracheo-oesophageal fistula
14	2 d	Tracheo-oesophageal fistula
15	2 d	Gastroschisis
16	14 d	Gastroschisis
17	3 d	Gastroschisis
18	2 d	Gastroschisis
19	2 d	Hirschsprung's disease
20	6 wk	Hirschsprung's disease
21	1 mth	Laparotomy: right cutaneous ureterostomy
22	10 mth	Laparotomy: colostomy
23	7 d	Laparotomy: necrotizing enterocolitis
24	5 d	Intestinal obstruction
25	1 mth	Intestinal obstruction
26	8 d	Ileal atresia
27	2 d	Ileal atresia; small bowel volvulus
28	10 wk	'Apple-peel' small bowel; multiple jejunal atresias
29	4 mth	Multiple small bowel adhesions
30	6 mth	Enteric duplication
31	6 d	Ladd's bands; malrotation of the mid-gut

The output of amylase was below the detectable limit (10 Somogyi units/day) in all controls and was detected at very low levels, far below the normal adult range, only on the first day in 4 patients after

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Table II: URINARY ALKALINE RIBONUCLEASE ACTIVITY AFTER CARDIAC SURGERY (Kunitz units 24 h^{-1} kg^{-1})

	Day after operation										
Case no.	1	2	3	4	5	6	7	8	9	10	*P*
1	2·7	3·4	4·3	2·9	2·2	1·2	1·0	0·5	0·5		<0·01
2	1·9	2·5	4·4	3·6	2·6	3·7	2·2	3·1	2·3	1·7	<0·001
3	1·4	1·3	3·0	3·6	1·8	1·3	1·2	0·8			<0·01
4	2·9	2·2	2·9	6·0	5·0	3·4	0·8	0·5	0·8	1·1	<0·01
5	2·2	1·0	1·0	1·3	2·8	0·8	2·3	1·7	1·8	1·2	<0·001
6	4·1	3·2	3·9	3·8	5·0	2·5	1·3	1·0	0·6	0·6	<0·01
7	0·2	1·2	1·5	1·4	1·1	0·7	0·8	0·2	0·2	0·3	n.s.
8	0·2	2·2	2·3	0·4	2·0	2·5	0·9	1·1			<0·02
9	4·7	1·4	5·1	6·8	6·1	6·7	3·7	1·7	1·3	0·9	<0·01
10	1·8	2·7	3·8	4·1	5·1	3·9	2·2	3·2	2·4	1·3	<0·001
11	2·1	3·5	3·6	3·7	4·8	5·4	3·2	1·5			<0·001

Normal levels, 0·43±0·29 Kunitz units 24 h^{-1} kg^{-1}.

Table III: EXCRETION OF ALKALINE RIBONUCLEASE BY NEONATES AND INFANTS UNDERGOING INTESTINAL SURGERY (Kunitz units 24 h^{-1} kg^{-1})

	Day after operation																
Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	*P*
12							0·2	0·1									n.s.
13				0·7	0·3	0·5	0·6	0·5	0·4	0·5							n.s.
14		1·1	0·6	0·9	1·3	0·7	1·7	1·1	1·2	0·7	1·7						<0·01
15		7·4	4·7	3·8	6·3	4·0	3·1	2·7	0·8	1·1	2·0	0·7	1·0	1·0	1·9		<0·01
16	3·4	2·0	3·4	3·9	1·9	3·3	2·5	1·7	1·7	1·3							<0·001
17			5·6	10·0	7·6	5·3	3·0	13·8	15·7	3·7	0·9	2·1					<0·001
18	1·0	0·6	0·6	0·5	0·4	0·7	1·2	1·2	0·9	0·8	1·0	0·3	0·7	0·2	0·6		<0·05
19	0·6	0·2	0·8	0·5	0·9	0·5	0·3	0·9	0·4	0·3							n.s.
20		0·6	1·1	1·4	0·7		0·5	0·8	0·7	0·9							<0·05
21	5·0	5·6	5·6	5·6	6·5	5·8	6·4										<0·001
22		6·0		2·9	2·6	0·7	1·2	1·1									<0·05
23			5·0	4·3	5·0	5·4	4·8	5·6	4·6	4·8	4·0	2·0	1·6	2·0	1·5	1·6	<0·001
24	1·1	1·6	1·7		1·4	2·1	1·5	1·6	1·0	1·4							<0·001
25	0·3	0·9		0·2					0·5	1·1	0·7	0·1	0·3				n.s.
26	1·2	1·6	1·6	1·0	1·4	0·8	0·4										<0·01
27	1·3		0·8	2·6	1·2	1·6	2·1	1·9	1·9								<0·001
28	0·3	0·6	0·7	0·9	1·7												n.s.
29	0·4		0·4	0·3	0·5												n.s.
30	1·9	1·0	0·9	1·1	1·1	2·2	1·3	1·7	0·7	1·0							<0·001
31	0·7	1·3	0·5	3·7	1·9	2·2	1·4	1·8	2·0	1·5							<0·01

Normal level, 0·43±0·29 Kunitz 24 h^{-1} kg^{-1}.

open heart operation. *P* values were calculated using the mean of all the observations in the group.

Discussion

Although Sigulem et al. (1973) found that the output of ribonuclease in the urine of neonates was lower than in children aged 7 months or more, we found that when these outputs were expressed in terms of body weight and the duration of the period of collection there were no significant differences between the neonates less than 15 days old and children over 10 months of age except in one normal premature baby (31 weeks' gestation) who had an unexplained high output; the results from this baby were at least five standard deviations above the mean.

Regardless of what kind of open operation was done on the heart, all patients except the one with the transposition of the great arteries (*Case* 7) showed a raised output of ribonuclease in the urine when this was averaged out over the days of the collections. In the one exception, although there was not an increase, overall excretion was high on 5 of the 10 days on which collections were made. In the 3 other patients with transposition of the great arteries the urinary excretion was raised but not by as much as in other patients after cardiac operations. With the one exception, the difference between the ribonuclease outputs after cardiac operations and those of normal patients was significant ($P<0·001$). In cases with transposition of the great arteries the patient is often cyanosed, with a low Po_2, and, having had the condition for some time, may well have become adapted to some extent, so that on operation, the effect on the ribonuclease excretion would be less than otherwise. If the total urinary excretion of ribonuclease averaged over the days of collection in patients who had open operations on the heart is compared with that of patients who had been accidentally burned the severity of the cardiac operations varies between the equivalent of a burn of 20 per cent of the body surface (*Case* 7) and 80 per cent of the body surface (*Case* 9). This should not, however, be taken as an accurate index of the severity of the surgical injury suffered by the patients undergoing major open operations on the heart, as there are surely a number of other factors that might influence the urinary output of ribonuclease. Many heart operations are carried out at subnormal body temperature with reduced blood flow to the pancreas.

There were some marked differences in ribonuclease excretion in the group of patients who were treated for various malformations of the gastrointestinal tract. It is surprising that 2 of the 3 patients who were treated for oesophageal atresia with tracheo-oesophageal fistula did not show increased ribonuclease excretion, and the third showed only a slight elevation. There were, however, significant increases in output in 4 babies with gastroschisis and in 3 who underwent laparotomy for various causes ($P<0{\cdot}05$).

The ribonuclease found in these urine samples had an optimum pH of 7·8, which was identical in normal children and in those having had an operation. This pH is indicative of an exocrine digestive function compatible with a pancreatic origin. In adults, when pancreatic disturbance is suspected it is usual to measure also the serum or urinary amylase concentrations. Urinary amylase in children, as we have shown, is not usually detectable, and when it was found in this series it might have been due to morphine given for the operation.

References

BARLOW G. B. and WHITEAR S. H. (1977) Urinary alkaline ribonuclease activity in children with burns and scalds. *Clin. Chim. Acta* **78**, 331–334.

FEINER H. (1976) Pancreatitis after cardiac surgery. A morphological study. *Am. J. Surg.* **131**, 684–688.

HENNINGS B. and JACOBSON G. (1974) Postoperative amylase excretion. A study following thoracic surgery with and without extracorporeal circulations. *Am. Clin. Res.* **6**, 215–222.

SIGULEM D. M., BRASAL J. A., VELASCO E. G. et al. (1973) Plasma and urine ribonuclease as a measure of the nutritional status in children. *Am. J. Clin. Nutr.* **26**, 793–797.

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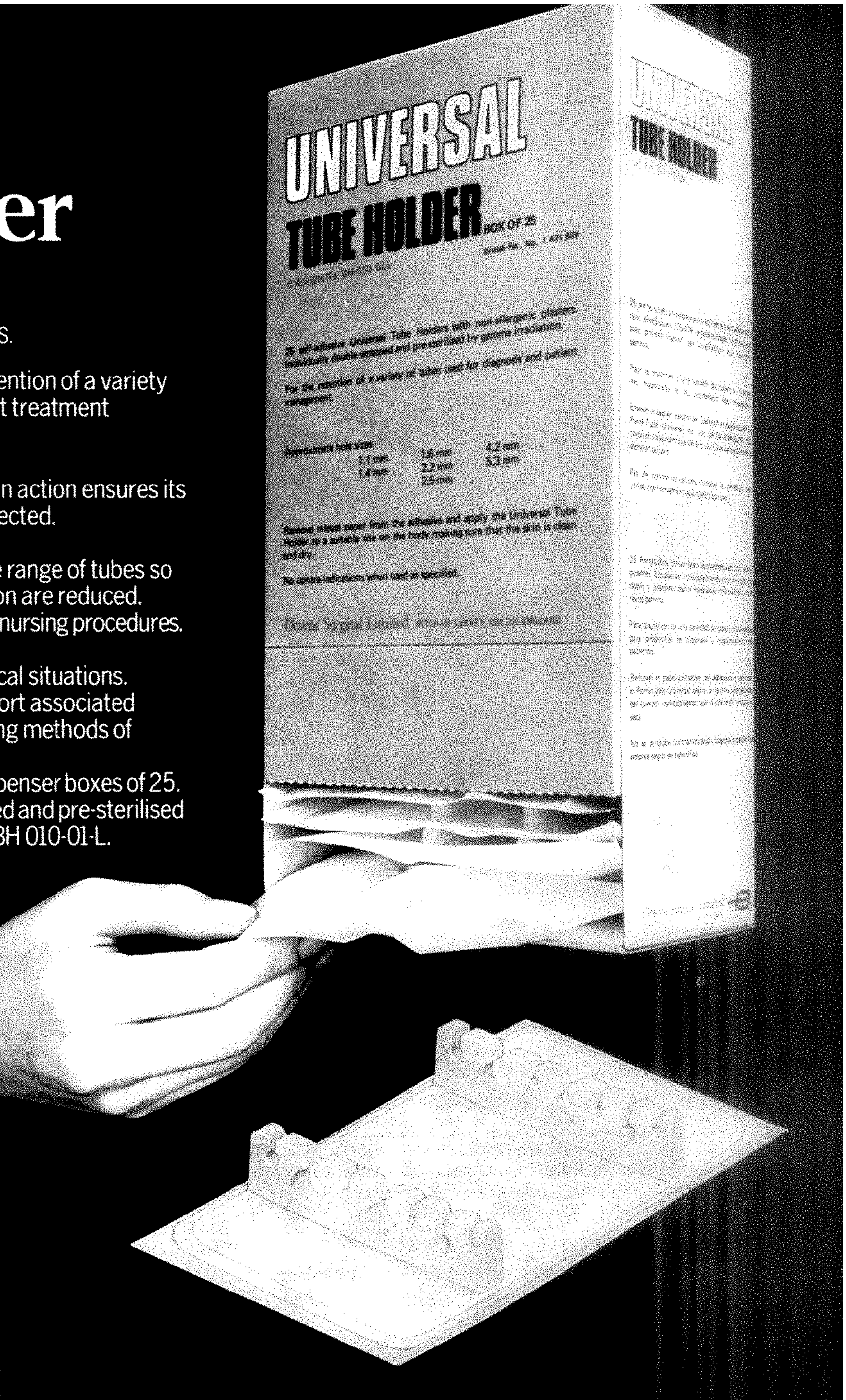

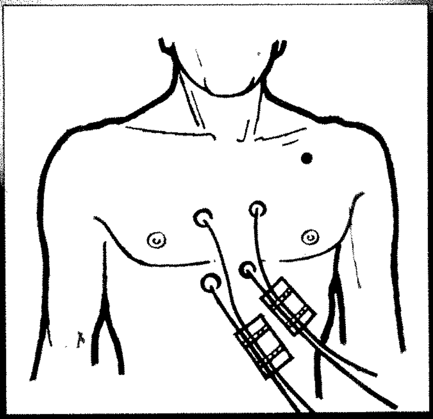

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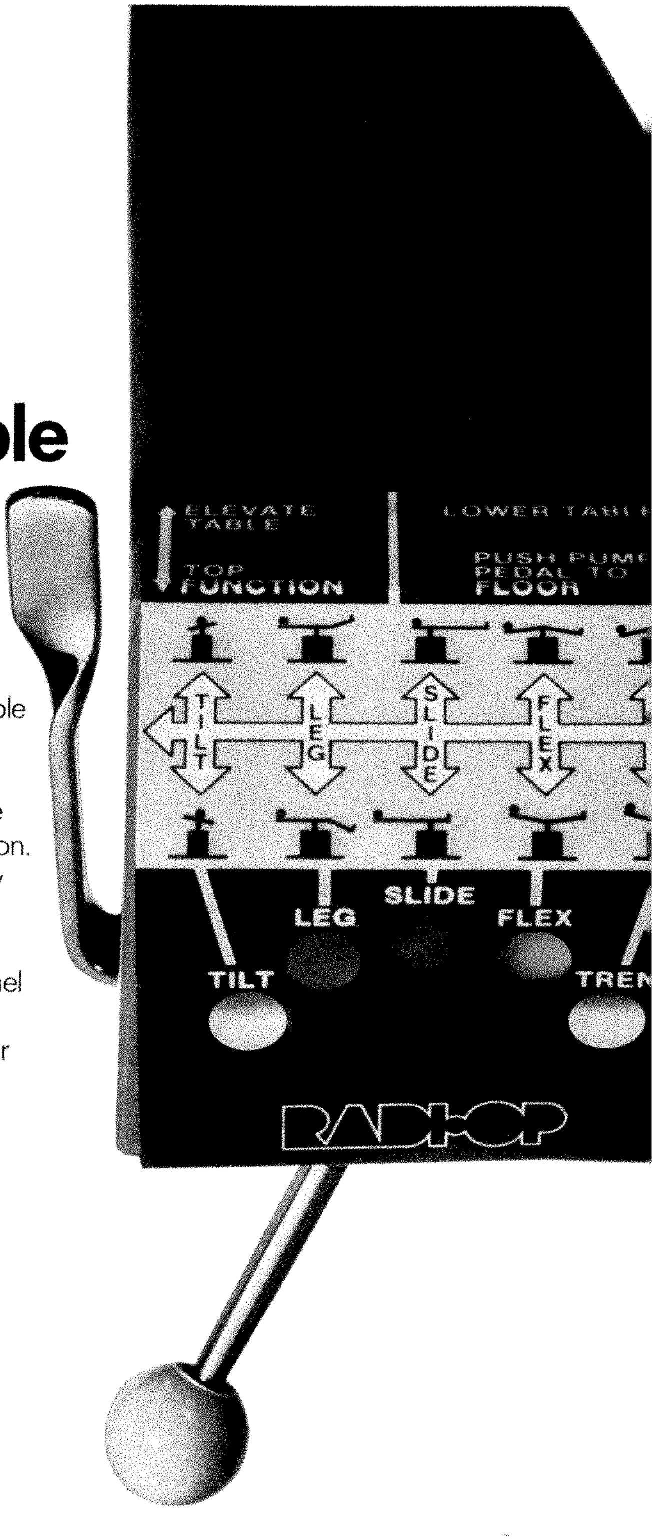

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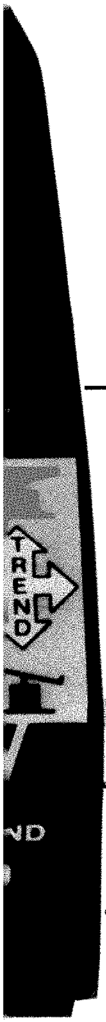

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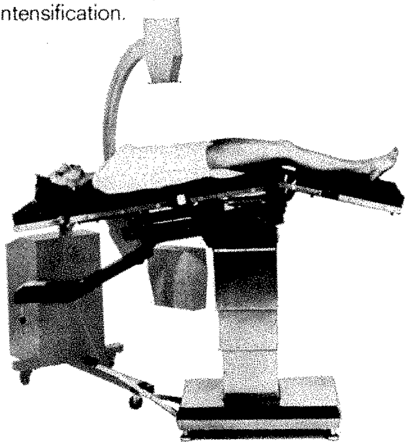

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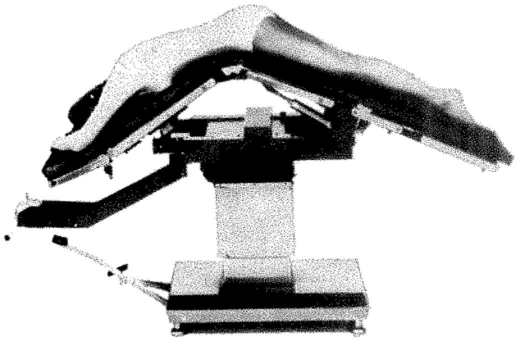
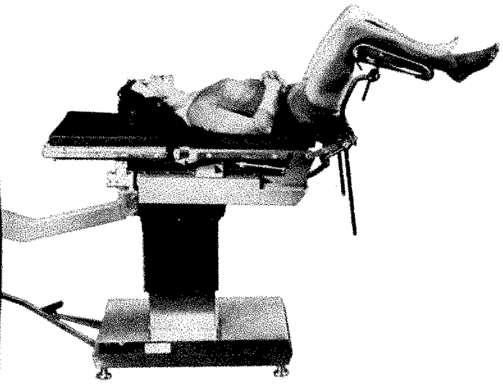
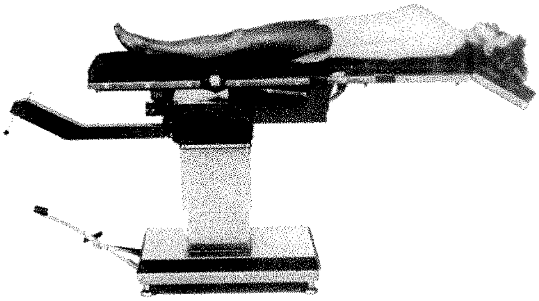


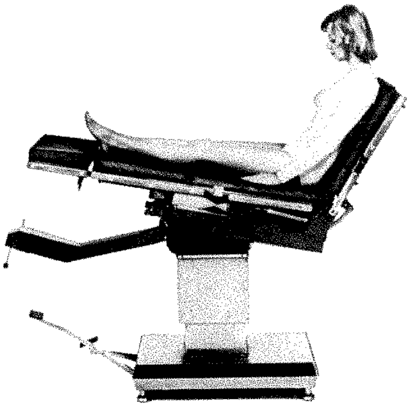
Lithotomy. The Radi-op table offers elevation of the pelvic area to provide access to the surgical site.



ENT. Total unobstructed access to the patient by the surgical team.



Neurosurgery. Unimpeded approach by the surgical team for all neurosurgical procedures performed in the sitting position.



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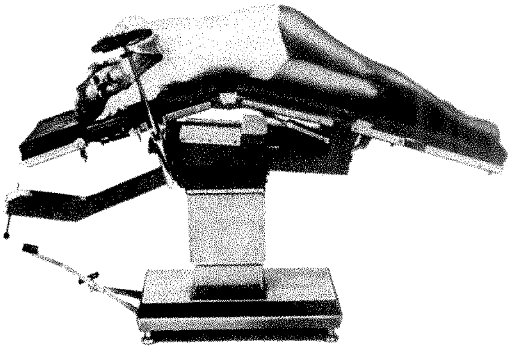

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Br. J. Surg. Vol. 66 (1979) 415–418

Eating patterns in patients recovering from major surgery—a study of voluntary food intake and energy balance

A. F. HACKETT, C. K. YEUNG AND G. L. HILL*

SUMMARY

Voluntary food intake (VFI) and energy balance were studied in 12 adult patients over a 2-week period following elective colectomy. Daily VFI was recorded by weighing all food presented to the patient as well as any rejected by him or her. Home VFI was estimated by a dietary history technique. Energy balance was calculated from the VFI and from the changes in body fat and protein that occurred over the study period.

The home VFI of the males was greater than that of the females with mean values of 2342 ± 542 kcal per day and 1666 ± 444 kcal per day respectively (mean ± 1 s.d.; $P<0{\cdot}05$).

Eleven patients began to eat 2–7 days after the operation, reaching a maximum VFI in stepwise fashion between 7 and 14 days. The maximum VFI reached during this period was related to the home VFI ($r = 0{\cdot}84$; $P<0{\cdot}01$). The twelfth patient required a second operation on the fifth postoperative day and began to eat 4 days later, reaching a maximum after a further 9 days.

No simple relationship was found between postoperative VFI and energy output over the study period. The higher the energy output, the more energy was derived from endogenous fat and protein. An average energy deficit of 1155 kcal per day (range +197 to −2758) was observed, and there was no significant relationship between this deficit and the VFI, which averaged 949 kcal per day (range 371–1833).

It is concluded that the amount of food consumed by post-surgical patients is dependent primarily on their previous home intake and not on their energy output. Patients with high energy outputs do not compensate by increasing VFI and large energy deficits can develop.

IN a recent study of surgical patients the average values for the various nutritional markers measured were changed in the direction of protein energy malnutrition (Hill et al., 1977). These changes were greatest in patients who had had a major surgical operation more than a week previously, many of whom had conditions which are known to increase energy output, such as sepsis or malignancy.

It is not known, however, if the magnitude of the energy deficit, i.e. the degree of malnutrition, is related to deficient food intake in the postoperative period. We therefore studied voluntary food intake (VFI) and energy balance in a group of patients recovering from a major surgical operation.

Patients and methods

Patients

Twelve patients (6 men and 6 women) admitted to the University Department of Surgery at the General Infirmary, Leeds, between September 1977 and April 1978, for elective major colorectal operations were studied. The men and women were on separate wards and only one observer (A. F. H.) was involved in assessing the VFI of all patients. Informed consent was obtained and no patient was lost to the study through lack of cooperation.

Table I shows the sex, age, preoperative body weight, diagnosis and the type of operation for each patient studied. All made an uncomplicated postoperative recovery, except for one (*Case* 3), who developed a leak from her ileorectal anastomosis on the fifth postoperative day. She underwent reoperation and an end-ileostomy was established. Her progress was then uncomplicated for the remainder of the period studied.

Home voluntary food intake

Pre-admission VFIs were assessed by a 7-day dietary history, giving an estimate of recent 'unusual consumption'. Portion size was recorded in household measures and later converted to grammes or millilitres. This record was then cross-checked against a comprehensive list of foods and weekly frequency of consumption (and portion size) was noted. The total weekly nutrient intake was divided by seven to give an arbitrary average daily intake.

Postoperative voluntary food intake

The VFI after surgery was assessed by weighing each dietary item presented to the patient and any items rejected by him or her. Drinks were assessed by volume, e.g. cupful. All patients were visited between each meal to assess any incidental intake of nutrients and such foods or duplicates were weighed whenever possible. Every effort was made to ensure that the patients studied were treated no differently from the other patients on the ward. The food intake was converted to nutrient intake using standard tables (McCance and Widdowson, 1973), and manufacturer's data where appropriate. By extrapolating from the work of Stock and Wheeler (1972), the overall error of this method for measuring VFI is approximately ±15 per cent.

Energy balance

This was calculated from the VFI and from the changes in body fat and body protein that occurred over the study period. The body tissue changes were measured using the method of Hill and his colleagues (1978). In brief, the patients were weighed and body fat was calculated from the thickness of the mid-biceps, mid-triceps and subscapular skinfolds (Durnin and Womersley, 1974). All the anthropometric measurements were made by one author (C. K. Y.). Total body nitrogen (TBN) was measured by *in vivo* neutron activation analysis and total body protein was calculated from this by multiplying by 6·25. Body weight, body fat and body protein were measured in each patient just before operation and 14·7 ± 1·8 days (range 11–16 days) after operation.

The changes in body composition were then considered in terms of their energy value, i.e. 1 g of fat = 9 kcal and 1 g of protein = 4 kcal. Energy output was then calculated according to the equation: Energy output = Energy intake (VFI) + Energy lost (loss of fat + loss of protein).

Results

Home VFI for energy was greater ($P<0{\cdot}05$) for the men (2342 ± 542 kcal) than for the women (1666 ± 444 kcal), although the average contribution of protein to the home energy intake was similar—13·3 ± 1·8 per cent for men and 13·7 ± 7·3 per cent for women.

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* University Department of Surgery, The General Infirmary, Leeds.

Table I: DETAILS OF THE PATIENTS STUDIED

Case	Sex	Age (yr)	Preop. weight (kg)	Diagnosis	Operation
1	F	24	56·4	Crohn's colitis	Subtotal colectomy with ileorectal anastomosis
2	F	62	59·5	Carcinoma of sigmoid colon	Sigmoid colectomy
3	F	70	59·2	1. Carcinoma of caecum 2. Ulcerative colitis	1. Colectomy with ileo-rectal anastomosis 2. Ileostomy
4	F	81	63·0	Carcinoma of rectum	Anterior resection
5	F	69	60·6	1. Cholelithiasis 2. Diverticulitis	Cholecystectomy and sigmoid colectomy
6	F	54	59·9	Carcinoma of lower sigmoid colon	Anterior resection
7	M	50	59·6	Carcinoma of rectum	Anterior resection
8	M	57	70·2	Carcinoma of rectum	Abdominoperineal excision of rectum
9	M	63	61·6	Carcinoma of rectum	Anterior resection
10	M	62	62·7	Carcinoma of descending colon	Left hemicolectomy
11	M	61	50·3	Carcinoma of caecum	Right hemicolectomy
12	M	54	50·5	Carcinoma of rectum	Anterior resection

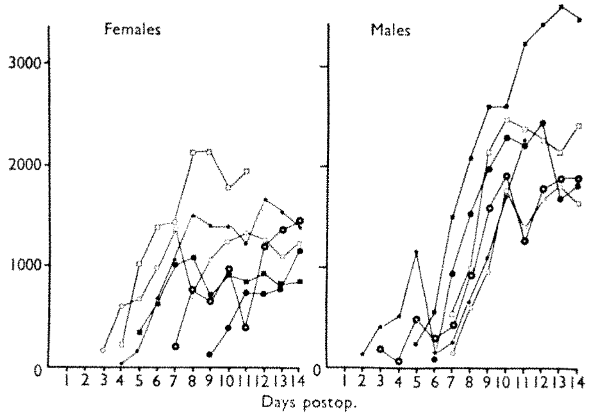

Fig. 1. Daily postoperative voluntary food intake (energy), in kilocalories per day.

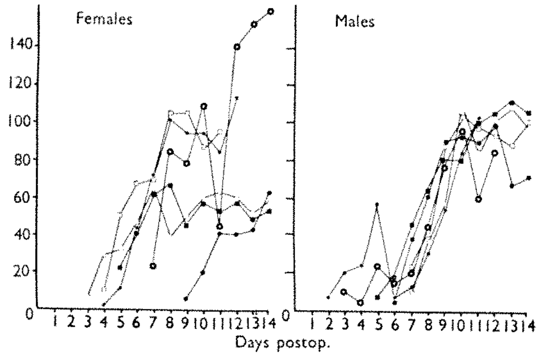

Fig. 2. Daily postoperative voluntary food intake (energy), this time expressed as a percentage of the estimated previous home voluntary food intake (energy).

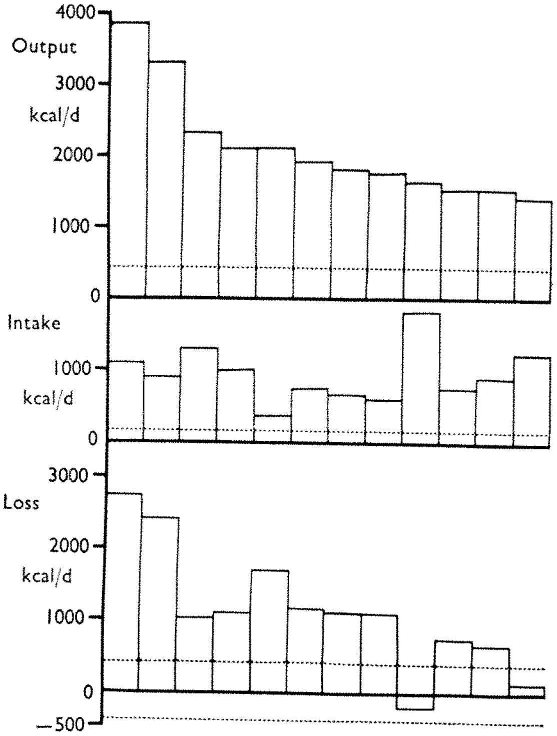

Fig. 3. Average energy balance for the period studied. The dotted lines indicate the maximum difference between the measurement, which can, with 95 per cent probability, be attributed to measurement error alone.

Home VFI was not related to body weight but there was a positive correlation with total body protein ($r = 0{\cdot}56$, $P < 0{\cdot}05$) and a negative correlation with total body fat ($r = -0{\cdot}80$, $P < 0{\cdot}01$).

Fig. 1 shows the daily postoperative VFI in terms of energy for each patient. All were in hospital for a minimum of 11 days after operation, but 7 were home by day 14. It can be seen that no patient consumed any nutrients on the first postoperative day and VFI commenced on an average of 4·7 days (range 1–9) after operation. All but one patient (*Case* 3, who had a further operation on postoperative day 5 and began eating 4 days later) were eating by day 7, the range at that time being 168–1504 kcal. Up until day 7 the intake of only 2 patients had exceeded 1000 kcal per day. By day 11 the range of VFI was 408–3218 kcal.

Fig. 2 shows the daily postoperative energy intake expressed as a percentage of the estimated home VFI. A stepwise increase in VFI occurred in most patients until the home VFI level was reached. Thereafter a strong tendency to maintain VFI at the home level was seen. Nine patients had reached their home VFI level by day 14, 1 patient (*Case* 3) reached this level on day 18 (13 days after her second operation) and the remaining 2, both females, maintained their VFIs at a level lower than their estimated home VFI.

The maximum 24-h energy intake up to postoperative day 11 was significantly correlated with the 24 h home VFI ($r = 0{\cdot}84$, $P < 0{\cdot}01$).

Fig. 3 shows the components of the average daily energy balance for each patient. It can be seen that energy intake was not related to energy output or energy lost. The average energy loss, or deficit, for the 2-week period studied was 16 176 kcal, ranging from a gain of 2950 kcal to a loss of 33 095 kcal; this approximates to an average loss of 1155 kcals per day.

Discussion

The mean home VFIs for men and women averaged only 78 per cent of the daily intake for energy recommended by the Department of Health and Social Security (1969). These standards, however, only strictly apply to populations of healthy people. Eight of our patients had lost between 6 per cent and 17 per cent of their pre-illness weight when they presented for operation. One patient with Crohn's colitis had been gaining weight prior to operation but this was probably due to the large dose of steroids which she was taking.

Most of our patients had cancer of the bowel. Weight loss in these patients is probably due to a combination of an inadequate food intake caused by factors such as anorexia, depression and abnormalities in taste sensation (DeWys and Walters, 1975) and an increased metabolic rate (Warnold et al., 1978). Although our method of estimating home VFI may be subject to systemic error, it does seem reasonable to conclude that home energy intake was inadequate to meet home energy expenditure for the majority of these patients and that it was less than the intake during health.

Home VFI was not found to be related to body weight; a finding that is in accord with the results summarized by Garrow (1974). However, a positive relationship was found with total body protein and a negative relationship with total body fat. This latter finding explains the absence of a correlation with body weight and is in keeping with the lipostatic theory of VFI control as reviewed by Andersson (1972).

Food intake, energy expenditure and balance have been measured a number of times before in surgical patients (Kinney et al., 1968). Such measurements have usually been made in a metabolic or other specialist unit. The food offered under these conditions is often very different in quantity and quality from that which the average ward patient receives. Nursing and medical attention, which are probably different on such units, may also influence VFI.

In the present study we have described the postoperative voluntary food intake of patients recovering from major colorectal operations in an ordinary ward. Food intake effectively ceases for approximately 5 days after this sort of surgery and then rises stepwise over 4–11 days to reach a maximum similar to the previous home VFI. In this way a considerable energy deficit is built up.

This study shows that energy intake in the early postoperative period was decided by habit and not by requirement (energy output). The overeating to 'repay' an energy deficit ('in a few days') observed by Adam and his colleagues (1957) in healthy active soldiers was not observed in these hospitalized patients over the period studied. Although the range of home VFIs was large (903–3268 kcal) and the food consumed in hospital was frequently different from that consumed at home, the patients were usually able to reach home levels of intake during the second postoperative week. This suggests that they were able to detect and regulate their energy intake on a relatively short term basis. Two female patients did not reach their estimated home VFI. For one there is some retrospective evidence of the home VFI being originally overestimated. The other was an 81-year-old woman who was a little vague about her eating habits. One female greatly exceeded her estimated home VFI, but she also had the lowest home VFI.

There were several complaints about the quality of the hospital food, and generally patients refused to eat much of the food offered to them (especially the women). The quality of the food, however, would not seem to be of much importance in determining postoperative hospital food intake. Conversely, the VFI may determine the patient's opinion of the food. Many patients apologized for leaving food and had to be reassured in order to protect the study. Generally the patients' evaluation of their food intake was found to be a very unreliable guide to what they actually ate.

We saw very few serious or effective attempts by the nursing staff (whose evaluation of VFI was often as poor as the patients) to improve the food intake of those patients consistently rejecting food.

The energy balance data showed that the patients with the greatest need for energy, i.e. those with the highest energy output, had proportionately least chance of meeting this need from VFI. Intake appeared unable to respond to the energy output over the 2-week postoperative period studied. In this way an appreciable energy deficit was created (range +197 to −2758 kcal per day) in most patients.

The calculated postoperative energy outputs for these patients are of the same magnitude as those reported by others (average 2102 kcal per day, range 1401–3850). Kinney et al. (1968) studied the energy balance of 10 major surgical cases. In their study the postoperative energy output, calculated from the estimated protein and fat losses, averaged 1498 kcal per day (range 1205–1798). The measured resting metabolic expenditure averaged 1396 kcal per day (range 1209–1663) and the energy intake averaged 884 kcal per day (range 451–1254). In the present study energy intake averaged 949 kcal per day (range 371–1833). Thus, the data from these two studies would seem to be quite comparable, although our patients had slightly higher energy outputs, which might reflect the extra exercise that is possible on a general ward, or more probably the increased magnitude of the surgical procedure undergone by our patients.

Our most important point is that the amount of food consumed by patients recovering from colorectal operations is dependent primarily on their previous home intake and not on their energy output. Patients with high energy outputs after major operations do not appear to be able to compensate by increasing food intake.

This work helps to explain how some patients with high energy expenditures develop protein energy malnutrition while recovering from major surgical procedures.

Acknowledgement

We would like to thank Mead Johnson Laboratories for their support of this project.

References

ADAM J. M. et al. (1957) Army Personnel Research Committee, Medical Research Council Report No. APRC 57/1, London, HMSO.

ANDERSSON B. (1972) *Handbook of Sensory Physiology III.* Berlin, Springer-Verlag, p. 84.

DEPARTMENT OF HEALTH AND SOCIAL SECURITY (1969) *Report on Public Health.* (Medical Subject No. 120.) London, HMSO.

DEWYS W. D. and WALTERS K. (1975) Abnormalities of taste sensation in cancer patients. *Cancer* **36**, 1888–1896.

DURNIN J. V. G. A. and WOMERSLEY J. (1974) Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br. J. Nutr.* **32**, 77–97.

GARROW J. S. (1974) *Energy Balance and Obesity in Man.* Amsterdam, North-Holland.

HILL G. L., BLACKETT R. L., PICKFORD I. et al. (1977) Malnutrition in surgical patients—an unrecognized problem. *Lancet* **1**, 689–692.

HILL G. L., MCCARTHY I. D., COLLINS J. P. et al. (1978) A new method for the rapid measurement of body composition in criticallyill surgical patients. *Br. J. Surg.* **65**, 732–735.

KINNEY J. M., LONG C. L., GUMP F. E. et al. (1968) Tissue composition of weight loss in surgical patients. I. Elective operation. *Ann. Surg.* **168**, 459–474.

MCCANCE R. A. and WIDDOWSON E. M. (1973) Medical Research Council Special Report, Serial No. 297. London, HMSO.

STOCK A. L. and WHEELER E. F. (1972) Evaluation of meals cooked by larger-scale methods: a comparison of chemical analysis and calculation from food tables. *Br. J. Nutr.* **27**, 439–448.

WARNOLD I., LUNDHOLM K. and SCHERSTEN T. (1978) Energy balance and body composition in cancer patients. *Cancer Res.* **38**, 1801–1807.

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A simple suction device for removing foreign bodies in the rectum

KENNETH STEVEN, JØRGEN LYKKE AND THOMAS STEENBERG HANSEN, *Department of Surgery K, Frederiksberg Hospital, Copenhagen, Denmark.*

WE describe here a simple, easily made suction device that has proved efficient for removing foreign bodies lodged in the rectum.

The device consists of two parts: a de Pezzer 34F-gauge catheter and an ordinary suction tubing set. The tip of the de Pezzer catheter is cut off, and the plastic end of the suction tubing set is inserted all the way through the de Pezzer catheter. The tubing fits tightly within the de Pezzer catheter, the cut end of which thus functions as a suction disc.

For use, the device is placed in contact with the foreign body in the rectum and suction is applied with a standard theatre sucker. After waiting for a few seconds to allow the pressure in the device to decrease, traction is applied to the de Pezzer catheter. Suction of about 600 mmHg—capable of lifting a full litre-bottle of saline by its base—can be obtained with an ordinary theatre sucker.

The device functions in an atraumatic manner because the diameter of the device is usually smaller than that of the foreign body. We have found this method to be of value, even for removing objects such as a bottle lodged in the rectum.

Accepted 6 November 1978.

Br. J. Surg. Vol. 66 (1979) 419–421

The Celestin tube in the palliation of carcinoma of the oesophagus and cardia

N. R. SAUNDERS*

SUMMARY

A series of 105 patients with dysphagia due to inoperable carcinoma of the oesophagus or cardia of the stomach, and 11 patients with dysphagia secondary to malignant mediastinal nodes, was treated by intubation with a Celestin tube. The hospital mortality was high but 81 patients left hospital and 29 were still alive at 6 months. The prognosis for those with dysphagia due to malignant posterior mediastinal nodes was very poor, with no survivors at 6 months. Oesophageal perforation was a serious operative complication, with a hospital mortality of 83 per cent. Chest and wound infections were the most common postoperative complications occurring in 28 and 20 per cent of the patients, respectively.

The restoration of swallowing was satisfactory in the majority of survivors although readmission with a blocked or displaced tube was not uncommon.

ALTHOUGH it is generally accepted that primary carcinomas of the lower oesophagus and cardia of the stomach are best treated by resection, 65 per cent of patients are inoperable at the time of their first consultation (Miller, 1962). Palliative procedures to relieve dysphagia are, therefore, of considerable importance and ideally these procedures should be both safe and simple. Bypass procedures have been tried by a number of authors (Allison and Borrie, 1949; Miller, 1962; Barnard et al., 1966; El Domeiri et al., 1970; Postlethwaite et al., 1971; Stephens, 1971), but the mortality from these operations may reach 60 per cent and the palliation is often unsatisfactory. Better results have been achieved by intubation of the malignant stricture, as first suggested by Leroy d'Etiolles of France in 1845 (Celestin, 1959). The first successful intubation was reported by Sir Charles Symonds in 1887, and since that time many different tubes have been used. In 1924 Souttar introduced a tube made of German silver wire with an expanded top which could be inserted via the oesophagoscope (Souttar, 1924, 1927). The next significant advance came in 1956 when Mousseau and Barbin introduced a neoplex tube which was inserted by a 'pullthrough' technique through a high gastrotomy (Mousseau et al., 1956) and then in 1959 Celestin introduced his modification of the Mousseau–Barbin tube. This had barrel-shaped proximal flange and a detachable pilot bougie of solid polythene. This tube is now widely used for palliative intubation of oesophageal neoplasms and a review of its use over a 10-year period is presented.

Patients and methods

Patients

Over a 10-year period (December 1967–October 1977) 105 patients (71 male, 34 female) with dysphagia secondary to carcinoma of the oesophagus or cardia, and 11 patients (10 male, 1 female) with dysphagia secondary to extrinsic compression of the oesophagus by malignant mediastinal nodes, were treated by intubation with a Celestin tube. The average duration of dysphagia before the first medical consultation was 6·4 months, but 1 patient waited 3 years before seeking treatment.

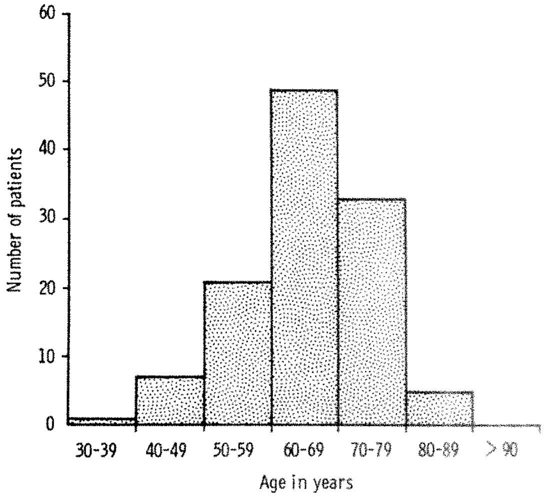

Fig. 1. Age distribution of patients in the series.

The average age was 65 years with a range of 37–86 (*Fig.* 1).

The site of the lesion was accurately defined in all cases and those with lesions arising at the oesophagogastric junction were classified as lower oesophageal (squamous) or cardiac (adenocarcinoma) depending on the histology. Twenty patients had lesions of the middle third of the oesophagus, 53 had lesions of the lower third and 28 had lesions of the cardia of the stomach. Four patients (3 male and 1 female) who had previously undergone oesophagogastrectomy for their malignancy developed dysphagia secondary to a recurrence at the anastomotic site and required Celestin tube intubation. Histological confirmation of the diagnosis was obtained in all cases.

The 11 patients with dysphagia secondary to extrinsic pressure on the oesophagus all had carcinoma of the bronchus with metastatic involvement of the posterior mediastinal nodes.

There were 2 cases of malignant tracheo-oesophageal fistula.

Technique

All patients underwent preliminary oesophagoscopy and biopsy. In 24 patients (21 per cent) the oesophageal tumour was considered operable on clinical, radiological and endoscopic grounds and inoperability was only established after exploratory thoracotomy in 18 patients and thoraco-abdominal exploration in 6.

In the remaining 92 patients (79 per cent) either inoperability was established at exploratory laparotomy or resection of the tumour was precluded due to advanced age or poor general health of the patient or the presence of distant metastases.

For those patients who underwent laparotomy by a left upper paramedian or upper midline incision, the Celestin tube was inserted as described by Celestin (1959) using a pullthrough technique and high gastrotomy. Tension sutures were used routinely in the closure of the abdominal wound.

In those who underwent thoracotomy alone a radial or circumferential incision in the diaphragm was made to gain access to the stomach for fixation of the distal end of the tube.

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Table I: MORTALITY

Time after intubation (mth)	No. deceased	%
1	39	34
3	62	53
6	87	75
9	100	86
12	108	93
15	114	98

Table II: MORBIDITY

Complication	No. of patients	%
Bronchopneumonia	33	28·4
Wound infection	23	19·8
Perforated oesophagus	12	10·3
Empyema	8	6·9
Blocked tube	4	3·4
Displaced tube	3	2·6
Intestinal obstruction	3	2·6
Subphrenic abscess	2	1·7
Gastric fistula	2	1·7

Dilatation of the malignant stricture was required in a number of patients before intubation with the Celestin tube.

Results

The 116 patients in this series were mostly elderly and many were debilitated as a result of the dysphagia and advanced malignancy. They thus represented a group of patients with an increased risk of both surgical and anaesthetic complications.

Mortality

Twenty-one patients (18 per cent) died within 7 days of operation including both patients with tracheo-oesophageal fistulas. The hospital mortality for the group was 30 per cent and the 3-month mortality, 53 per cent (*Table I*). Twenty-nine patients survived for longer than 6 months and achieved reasonable palliation, and the longest survivor died 28 months after insertion of his tube.

The prognosis for those patients with dysphagia secondary to posterior mediastinal deposits was worse than for those with dysphagia secondary to carcinoma of the oesophagus or cardia. The hospital mortality in the former group was 45 per cent and there were no survivors at 6 months.

The commonest causes of death were bronchopneumonia and metastatic spread of tumour.

Morbidity (*Table II*)

Bronchopneumonia was the commonest postoperative complication, occurring in 28 per cent of patients.

The relatively high incidence of wound infection—20 per cent of patients—was probably related to the difficulty in maintaining a sterile operative field during insertion of the tube. Most infections were superficial, and there were no cases of complete wound disruption in the series. The routine use of tension sutures in abdominal wound closure is believed to be an important factor in preventing this serious complication.

The oesophagus was perforated at the time of intubation in 12 patients (10 per cent) and in 8 of these subsequent drainage of an empyema was necessary. Only 2 of these patients left hospital and both died within 2 months. The mean survival of the remaining 10 patients in this group was 13 days.

In 3 cases the Celestin tube became displaced in the postoperative period and repositioning was necessary to prevent recurrent dysphagia; and in 4 patients the tube became blocked within 14 days of insertion and required clearing endoscopically.

The mean length of hospital admission was 19 days and those patients who left hospital achieved satisfactory palliation. They were able to swallow liquids and a semi-solid diet but tube blockage was a common cause of readmission. Twelve patients were readmitted once with a blocked tube and 4 patients had two or more readmissions. Reflux did not appear to be a major problem.

Late displacement of the Celestin tube was an uncommon complication, but when it did occur reoperation was normally necessary. In this series 11 patients (8 per cent) required reoperation for blocked or displaced tubes.

Discussion

The overall 5-year survival rate from malignant oesophageal obstruction varies from 1 to 9 per cent depending on the series quoted (Gunnlaugsson et al., 1970; Leon et al., 1971; Hankins et al., 1972). These poor figures are, in part, related to the fact that in most series two-thirds of the patients are inoperable when first seen. It is against this background that the survival figures of any palliative procedures must be measured.

Carcinoma of the oesophagus makes up 2 per cent of all malignant tumours and since 91 per cent of patients with this disease develop dysphagia (Parker et al., 1952), safe and simple procedures to restore swallowing are of considerable importance.

Various authors report operative mortalities of 10–28 per cent for oesophageal intubation by the pull-through technique and the 18 per cent operative mortality of this series is within that range. These figures compare favourably with those for various bypass procedures and palliative resections, in which the operative mortality is generally higher (10–60 per cent) and the palliation achieved often unsatisfactory (Allison and Borrie, 1949; Barnard et al., 1966; El Domeiri et al., 1970; Postlethwaite et al., 1971; Stephens, 1971).

In 1968 Plested et al. reviewed 12 000 reported cases of malignant oesophageal obstruction and found that 85 per cent died within 1 year regardless of therapy. With this prognosis it is important that restoration of swallowing is achieved quickly and simply and the patient's hospital admission kept to a minimum. In this series 81 patients (70 per cent) left hospital, having spent on average 19 days as inpatients. Of these, 29 patients (42 per cent) were still alive at 6 months and were without significant dysphagia, thus confirming successful palliation in this group.

When intubation is used to palliate dysphagia due to metastatic deposits in mediastinal nodes, the prognosis is very poor (Provan, 1969), with a hospital mortality of 45 per cent. However, in our series of 11 patients, 6 left hospital following intubation and 2 survived for 5 months, indicating that reasonable palliation can be achieved in this group also.

The insertion of a Celestin tube by the pullthrough technique involves a laparotomy and gastrotomy and these manoeuvres contribute significantly to the high hospital mortality and morbidity associated with the procedure. Recently the technique of fibreoptic endoscopic palliative intubation of oesophagogastric neoplasms with a Celestin tube has been reported (Atkinson and Ferguson, 1977). This procedure, which avoids a laparotomy, is associated with a reduction in morbidity and hospital mortality and a shorter hospital admission than the conventional pullthrough technique, although the long term outlook remains unaltered. Whichever method of intubation is used, a significant proportion of patients achieves reasonable palliation in terms of increased length and quality of survival.

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Bibliography

ALLISON P. R. and BORRIE J. (1949) The treatment of malignant obstruction of the cardia. *Br. J. Surg.* **37**, 1–21.

AMMANN J. F. and COLLIS J. LEIGH (1971) Palliative intubation of the oesophagus: analysis of 59 cases. *J. Thorac. Cardiovasc. Surg.* **61**, 863–869.

ATKINSON M. and FERGUSON R. (1977) Fibreoptic endoscopic palliative intubation of inoperable oesophagogastric neoplasms. *Br. Med. J.* **1**, 266–267.

BARNARD P. M., KILROY E. G. and KENNEDY J. H. (1966) Inoperable cancer of the oesophagus: use of the Mousseau–Barbin tube in palliative surgery. *J. Thorac. Cardiovasc. Surg.* **51**, 125–130.

CARTER R. and HINSHAW D. B. (1963) Use of the Celestin indwelling plastic tube for inoperable carcinoma of the oesophagus and cardiac. *Surg. Gynecol. Obstet.* **117**, 641–644.

CELESTIN L. R. (1959) Permanent intubation in inoperable cancer of the oesophagus and cardia. *Ann. R. Coll. Surg. Engl.* **25**, 165–170.

DAS S. K. and JOHN H. T. (1973) Oesophageal intubation in obstructive lesions of the oesophagus. *Br. J. Surg.* **60**, 403–406.

EL-DOMEIRI A., MARTINI N. and BEATTIE E. J. (1970) Esophageal reconstruction by colon interposition. *Arch. Surg.* **100**, 358–362.

GUNNLAUGSSON G. H., WYCHULIS A. R., ROLAND C. et al. (1970) Analysis of the records of 1657 patients with carcinoma of the esophagus and cardia of the stomach. *Surg. Gynecol. Obstet.* **130**, 997–1005.

HAIDERER O., MASRI Z. H., GIRADET R. E. et al. (1974) Palliation of advanced esophageal carcinoma by permanent intubation. *J. Thorac. Cardiovasc. Surg.* **67**, 491–495.

HANKINS J. R., COLE F. N., WARD W. et al. (1972) Carcinoma of the esophagus: the philosophy for palliation. *Ann. Thorac. Surg.* **14**, 2.

HOLDEN M. P., WOOLER G. H. and IONESCU M. I. (1973) Mousseau–Barbin tubes for the treatment of carcinoma of the lower two-thirds of the oesophagus. *Br. J. Surg.* **60**, 401–402.

LEON W., STRUG L. H. and BRICKMAN I. D. (1971) Carcinoma of the oesophagus: a disaster. *Ann. Thorac. Surg.* **11**, 583–592.

MILLER C. (1962) Carcinoma of the thoracic-oesophagus and cardia. *Br. J. Surg.* **49**, 507–522.

MOUSSEAU M. M., LE FORESTIER J., BARBIN J. et al. (1956) Place de l'intubation à demeure dans le traitement palliatif du cancer de l'œsophage. *Arch Mal. App. Dig.* **45**, 208–214.

PARKER E. F., HANNA C. B. and POSTLETHWAITE R. W. (1952) Carcinoma of the esophagus. *Ann. Surg.* **135**, 697–708.

PINDER G. C. and STANTON R. H. (1973) Prosthetic tubes in carcinoma of the esophagus; a definite place. *Chest* **63**, 586–589.

PLESTED W. C., TILDON T. T. and HUGHES R. K. (1968) A philosophy of treatment of esophageal carcinoma. *Am. J. Surg.* **34**, 650–656.

POSTLETHWAITE R. W., SEALY W. C., DILLON M. L. et al. (1971) Colon interposition for esophageal substitution. *Ann. Thorac. Surg.* **12**, 89–109.

PROVAN J. L. (1969) Use of Celestin tube for palliation of malignant oesophageal obstruction. *Thorax* **24**, 599–602.

SOUTTAR H. S. (1924) A method of intubating the oesophagus for malignant stricture. *Br. Med. J.* **1**, 782–783.

SOUTTAR H. S. (1927) Treatment of carcinoma of the oesophagus based on 100 personal cases and 18 post-mortem reports. *Br. J. Surg.* **15**, 76–94.

STEPHENS H. B. (1971) Colon bypass of the esophagus. *Am. J. Surg.* **122**, 217–222.

SYMONDS C. J. (1887) The treatment of malignant stricture of the oesophagus by tubage or permanent catheterism. *Br. Med. J.* **1**, 870–873.

THOMAS A. N. (1974) Treatment of malignant esophageal obstruction by endo-esophageal intubation. *Am. J. Surg.* **128**, 306–314.

VENNERT K. R. V. (1965) Epidermoid carcinoma of the esophagus: review of 150 cases. *Am. J. Surg.* **31**, 487–492.

WADDINGTON J. K. and BICKFORD B. J. (1962) Use of Mousseau–Barbin tube for palliation in carcinoma of the oesophagus and cardia. *Br. J. Surg.* **49**, 522–527.

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The role of thrombolytic therapy in the management of phlegmasia caerulea dolens

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SUMMARY

Two cases of phlegmasia caerulea dolens with peripheral venous gangrene treated with streptokinase are presented. Both patients had excellent results, beyond expectation. The literature is reviewed and the symptomatology, aetiology, pathogenesis and current thoughts on treatment are discussed.

PHLEGMASIA caerulea dolens is a rare, but potentially lethal, form of venous thrombotic disease. It is reversible, but may result in gangrene, pulmonary embolism or even death. Other terms describing the same entity include blue phlebitis ('la phlebité bleu de Grégoire') or acute massive venous thrombosis. The most severe form of this disease is venous gangrene. Haimovici (1966) groups phlegmasia caerulea dolens and venous gangrene under the heading of 'ischaemic thrombophlebitis', as the dominant manifestation is tissue ischaemia. In caerulea dolens the ischaemic changes are reversible as opposed to those of venous gangrene. The basic pathological condition in caerulea dolens is near total venous thrombotic occlusion, whereas in venous gangrene, there is total occlusion. In spite of being recognized for some 400 years, caerulea dolens still has a mortality of approximately 25 per cent and an amputation incidence of 50 per cent. Treatment has evolved from conservative medical management to venous thrombectomy, which has produced some improvement in immediate results. Since 1970 several reports (Paquet et al., 1970; Tsapogas et al., 1973; Roberts, 1976) have shown excellent results after treatment of caerulea dolens with streptokinase. In view of this and also because of the known poor long term results after thrombectomy (Lansing and Davis, 1968; Johansson et al., 1973), we used streptokinase in the treatment of 2 recent cases of caerulea dolens with venous gangrene, with extremely satisfactory results.

Case reports

Case 1: A 43-year-old female developed an iliofemoral thrombosis in her left leg. She was treated with heparin for 7 days and then given warfarin. On the third day of warfarin therapy, when the prothrombin index was 36 per cent, she developed severe pain in her left leg, which was uncontrolled even with heavy doses of morphine. Eight hours later the forefoot was cold and blue. A tentative diagnosis of an acute arterial occlusion was made and she was transferred to Groote Schuur Hospital. On arrival her temperature was 38·5 °C, respiration 38/min, pulse 148/min and her blood pressure was 140/80 mmHg. Local examination revealed the left leg to be grossly swollen to above the inguinal ligament and the lower leg mottled and blue. The distal left foot was blue-black and anaesthetic (*Fig.* 1). No movement was possible at either the ankle or the knee joint due to the oedema and extreme pain. No pulses could be detected in this limb, but Doppler examination revealed that all were audible, though diminished.

A diagnosis of massive venous occlusion with peripheral venous gangrene was made. The leg was elevated, intravenous penicillin given and streptokinase (Kabikinase, AB Kabi, Stockholm) therapy commenced using the manufacturer's recommended dosage. Within 24 h the patient's general and local condition had improved markedly (temperature 36·5 °C, pulse 90/min, respiration 22/min). The swelling was significantly reduced and all pulses were palpable (*Fig.* 2).

Haematological assessment at this time revealed satisfactory thrombolysis—fibrinogen 18 mg/100 ml, fibrin degradation products 320>640 μg/ml, thrombin time 23 s (control 10 s). Streptokinase therapy was continued for 72 h and the patient was then treated with heparin intravenously for a further 14 days. A venogram was then performed which showed occlusion of the iliofemoral system and warfarin sodium therapy was commenced shortly afterwards. The first and second toes were later amputated and a secondary closure performed. Six months later the leg appeared normal, with no evidence of oedema.

Case 2: An 18-year-old female in the 36th week of her pregnancy presented with a 12-day history of a left iliofemoral venous thrombosis. A bilateral venogram was performed which showed occlusive iliofemoral clot on the left. The patient was heparinized (10 000 units intravenously 6-hourly) and the clotting times were carefully controlled. Following delivery 12 days later, warfarin sodium therapy was commenced.

Six days later, the patient complained of severe pain in the left leg. On examination the leg was grossly swollen to above the inguinal ligament. No pulses were palpable below the left femoral. The three medial toes showed evidence of severe ischaemia and were anaesthetic (*Fig.* 3). A diagnosis of phlegmasia caerulea dolens with peripheral venous gangrene was made. (The prothrombin index at the time was 46 per cent.)

The leg was elevated, intravenous penicillin given and streptokinase therapy commenced. Twenty-four hours later the leg had improved markedly (*Fig.* 4), with only the first toe now being anaesthetic. Haematological assessment at the time showed evidence of satisfactory thrombolysis and the treatment was continued as in *Case* 1. A venogram was performed after 2 weeks which showed thrombosis of the deep venous system. Shortly afterwards the first toe and distal phalanx of the second toe were amputated. Three months later the patient had minimal oedema which was completely controlled using TED anti-embolism stockings (Kendall Company, Hospital Products).

Discussion

Massive oedema, cyanosis, excruciating pain, shock and the absence of peripheral pulses are all classic manifestations of phlegmasia caerulea dolens. This condition may occur at any age, but is commonest in the sixth decade. The two sexes are equally affected and the left lower limb is involved almost three times as often as the right. The upper limb is affected in about 5 per cent of cases.

It is clear from the literature that this condition almost always develops as a complication of another disorder. In approximately half the cases the primary pathology is carcinoma or inflammatory conditions or cardiac disease. The malignancies appear to be mainly localized to the gastrointestinal tract, whilst the inflammations appear to be equally distributed

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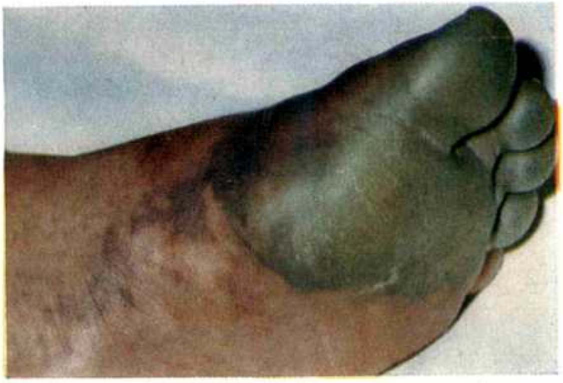

Fig. 1. *Case* 1. On presentation: mottling of the left foot with blue–black discoloration of the medial four toes.

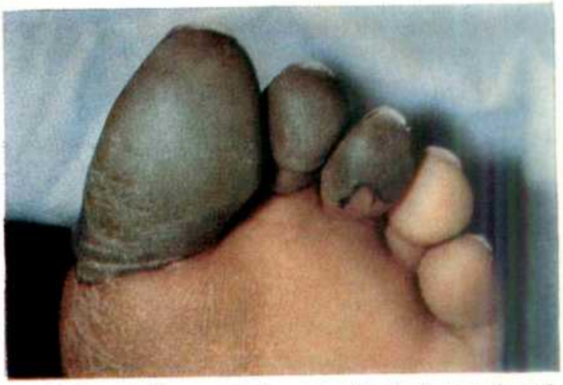

Fig. 3. *Case* 2. On presentation: blue–black discoloration of the medial three toes.

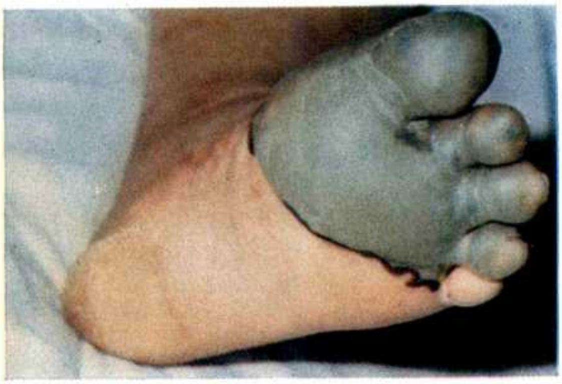

Fig. 2. *Case* 1. Twenty-four hours after commencement of streptokinase infusion. The lateral three toes appear viable.

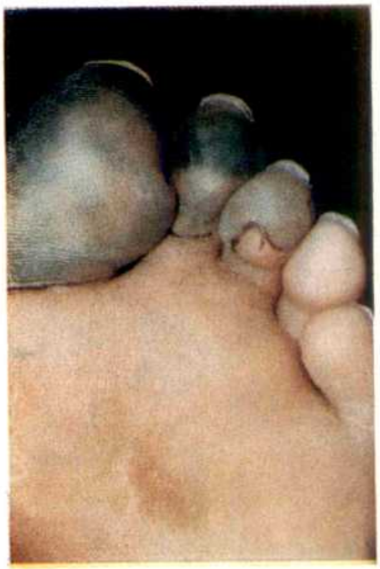

Fig. 4. *Case* 2. Twenty-four hours after commencement of streptokinase infusion. The vascularity of all the toes has markedly improved.

between the respiratory and alimentary systems. The postpartum (Moore and Scott, 1956) and postoperative states (Stallworth et al., 1965) precede the development of caerulea dolens in approximately 30 per cent of cases. In 60 per cent of cases the symptoms of caerulea dolens are preceded by the more common form of venous thrombosis, phlegmasia alba dolens (Haimovici, 1966). The time lapse appears to vary from a few days to several weeks.

Past treatment of this condition has included heparin (Anlyan and Hart, 1957), sympathetic blockade (Martin, 1953), rapid passive exercise (Veal et al., 1951) and fasciotomy (Cywes and Louw, 1962).

Thrombectomy was first used in the treatment of phlegmasia caerulea dolens by Leriche in 1939. Since this time many reports of this treatment have been published (Haller, 1961; Fogarty et al., 1963). It is apparent, however, that if a satisfactory result is to be achieved, the peripheral venous capillary system must be only partly involved (Brockman and Vasko, 1965). Haimovici (1966) later confirmed this and showed that the results of thrombectomy, once peripheral gangrene had developed, were unimpressive. It is universally agreed that in caerulea dolens, thrombectomy requires a general anaesthetic and may require wide exposure of the femoroiliocaval system. Therefore, this procedure cannot be considered in the desperately ill patient, which is all too frequently the case. Reports indicate that failures occur as often as successes. The failures appear to be due to rethrombosis and pulmonary embolism, but above all to an inability to remove thrombus from the tributary veins. Even if the thrombectomy is successful, one knows from Lansing and Davis (1968) and Johannson et al. (1973) that the patient will almost certainly develop post-phlebitic sequelae.

The first report of caerulea dolens treated successfully with streptokinase was published by Paquet et al. in 1970. They described 10 cases, of which 9 had excellent results. There was no incidence of pulmonary embolism, gangrene or death. Tsapogas et al. (1973) and Roberts (1976) later described single cases treated with streptokinase, again with excellent results.

Fibrinolytic therapy offers two important advantages over surgery: it will dissolve the multiple peripheral thrombi inaccessible to thrombectomy and no anaesthesia is necessary. It must be accepted that neither thrombectomy nor streptokinase is suitable for treating ageing, adherent thrombus. In the 2 cases we have reported, the lengths of history of iliofemoral thrombosis were 10 and 30 days respectively. It was felt that in both cases surgery would be unsuccessful owing to the adherence of the thrombus lying in the main venous channels. At the same time it was obvious that the peripheral skin infarction was of a short duration and therefore that thrombosis in the tributary veins might be amenable to fibrinolytic therapy.

In conclusion, we have confirmed that phlegmasia caerulea dolens can be successfully treated with streptokinase. We would stress that in order to avoid the bleeding complications of thrombolytic therapy, this drug should not be used within 10 days of major surgery, or even longer after vascular, neurosurgical or eye operations. Its use should be restricted to the hospital environment as it requires expertise and careful attention to the mode of administration.

Acknowledgements

These two cases form part of a larger study, funding of which from the South African Medical Research Council, University of Cape Town Staff Research Grants, the Nellie Atkinson Bequest and the Harry Crossley Foundation is gratefully acknowledged.

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References

ANLYAN W. G. and HART D. (1957) Special problems in venous thromboembolism. *Ann. Surg.* **146**, 499–509.

BROCKMAN S. K. and VASKO J. S. (1965) Observations on the pathophysiology and treatment of phlegmasia caerulea dolens with special reference to thrombectomy. *Am. J. Surg.* **109**, 485–492.

CYWES S. and LOUW J. H. (1962) Phlegmasia caerulea dolens: successful treatment by relieving fasciotomy. *Surgery* **51**, 169–176.

FOGARTY T. J., CRANLEY J. J., KRAUSE R. J. et al. (1963) Surgical management of phlegmasia caerulea dolens. *Arch. Surg.* **86**, 256–263.

HAIMOVICI H. (1966) The ischaemic forms of venous thrombosis. 1. Phlegmasia caerulea dolens. 2. Venous gangrene. *J. Cardiovasc. Surg.* (*Torino*) Suppl. 1, pp. 164–173.

HALLER A. J. (1961) Thrombectomy for acute ilio-femoral venous thrombosis. *Arch. Surg.* **83**, 448–457.

JOHANNSON E., NORDLANDER S. and ZETTERQUIST S. (1973) Venous thrombectomy in the lower extremity—clinical phlebographic and plethysmographic evaluation of early and late results. *Acta Chir. Scand.* **139**, 511–516.

LANSING A. M. and DAVIS W. M. (1968) Five year follow-up study of iliofemoral vein thrombosis. *Am. Surg.* **168**, 620–628.

MARTIN P. (1953) Phlegmasia caerulea dolens. *Br. Med. J.* **2**, 1351–1353.

MOORE R. F. and SCOTT G. B. D. (1956) Gangrene of venous origin. *Br. J. Surg.* **43**, 591–594.

PAQUET K. J., POPOV S. and EGLI H. (1970) Richtlinien und Ergebnisse der konsequenten fibrinolytischen Therapie der Phlegmasia caerulea dolens. *Dtsch. Med. Wochenschr.* **16**, 903–904.

ROBERTS W. M. (1976) Some clinical problems in patients undergoing thrombolytic therapy. *S. Afr. Med. J.* **50**, 243–247.

STALLWORTH J. M., BRADHAM G. B., KLETKE R. R. et al. (1965) Phlegmasia caerulea dolens. *Ann. Surg.* **161**, 802–811.

TSAPOGAS M. J., PEABODY R. A., WU K. T. et al. (1973) Controlled study of thrombolytic therapy in deep vein thrombosis. *Surgery* **74**, 973–984.

VEAL J. R., DUGAN T. J., JAMISON W. J. et al. (1951) Acute massive venous occlusion of the lower extremities. *Surgery* **29**, 355–364.

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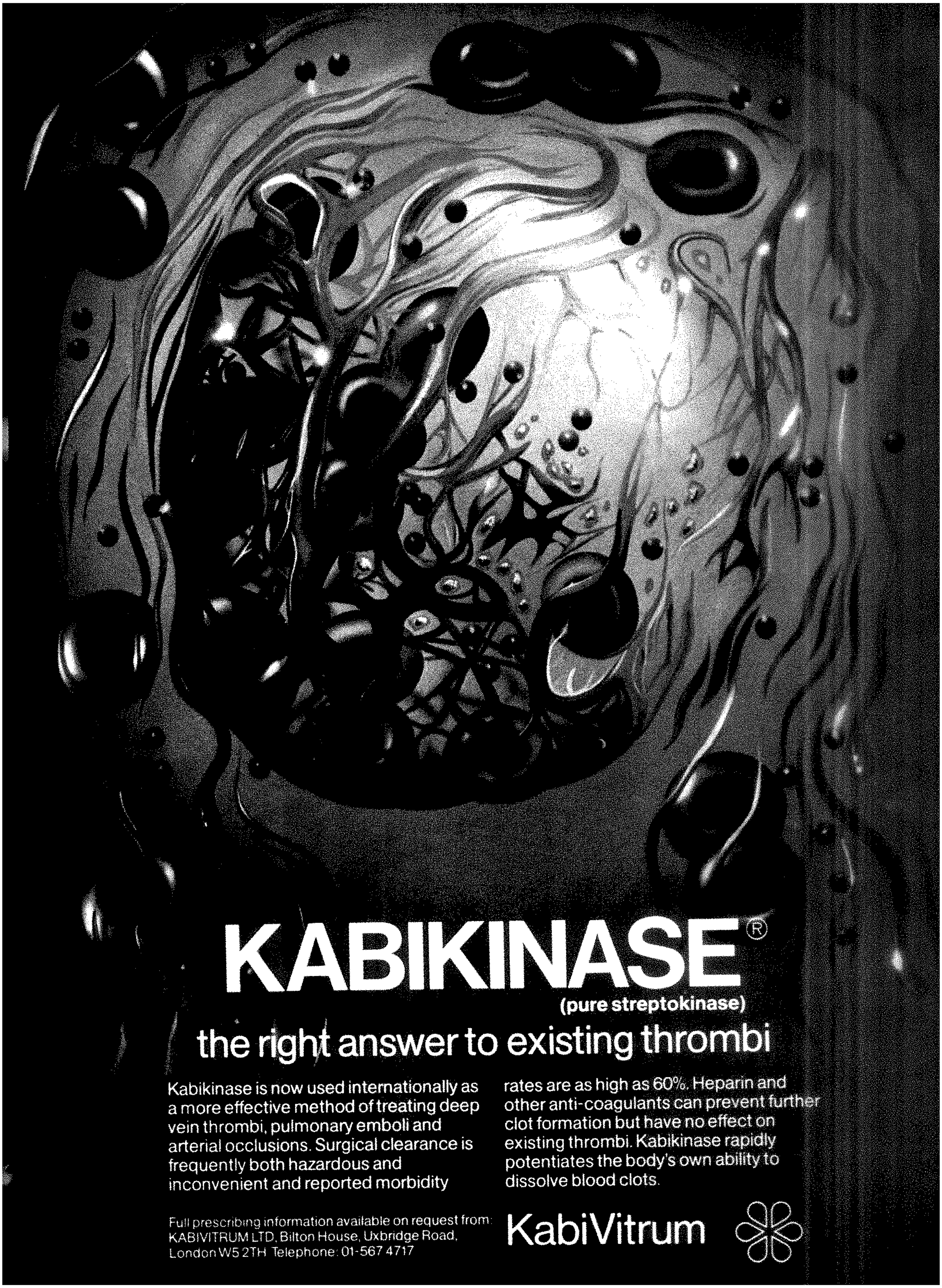

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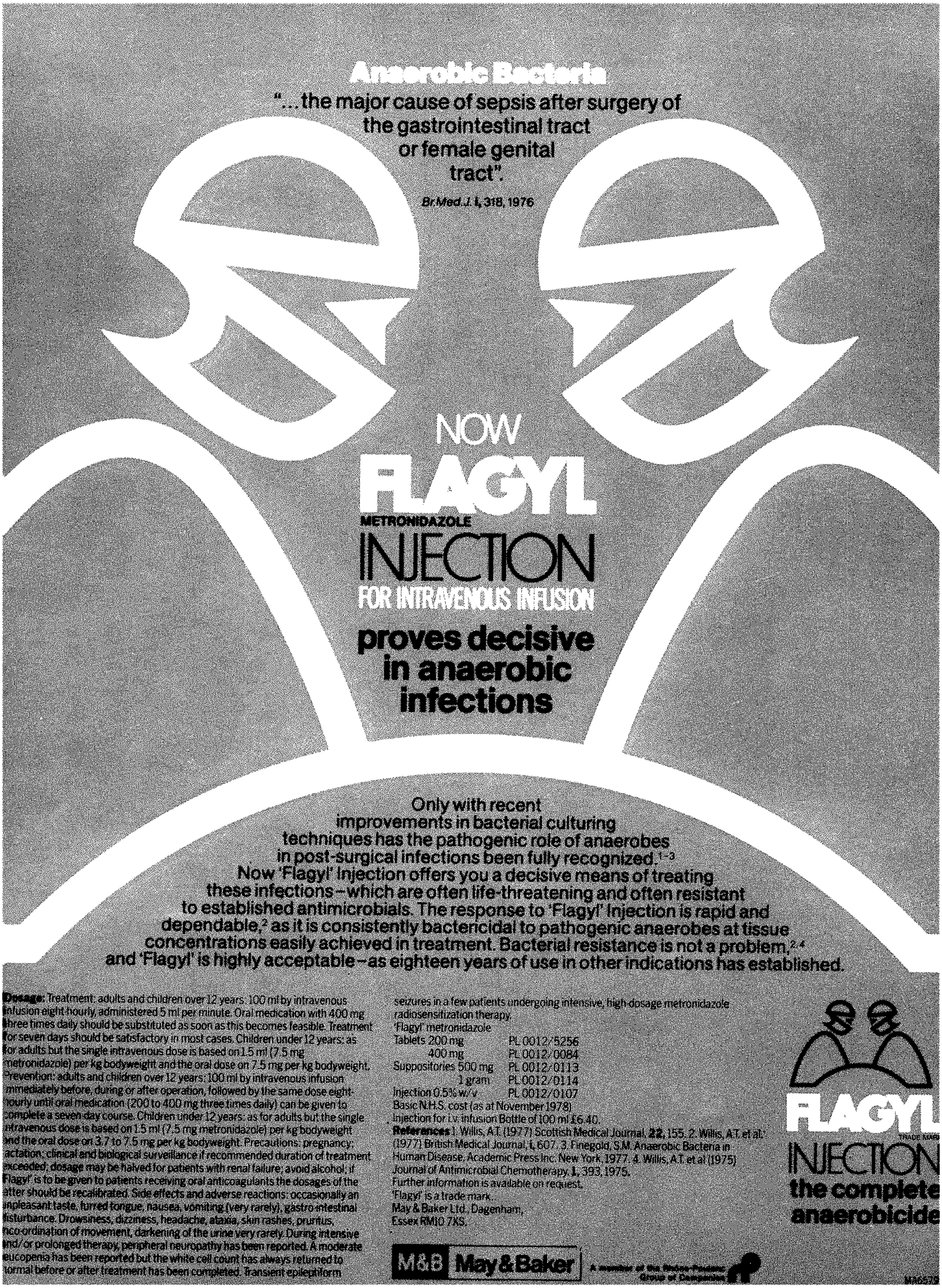

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References 1. Willis, A.T. (1977) Scottish Medical Journal, **22**, 155. 2. Willis, A.T. et al: (1977) British Medical Journal, **i**, 607. 3. Finegold, S.M. Anaerobic Bacteria in Human Disease, Academic Press Inc. New York, 1977. 4. Willis, A.T. et al (1975) Journal of Antimicrobial Chemotherapy, **1**, 393, 1975.

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Intrarectal metronidazole in the prevention of anaerobic infections after emergency appendicectomy: a controlled clinical trial

J. RODGERS, D. ROSS, W. MCNAUGHT AND G. GILLESPIE*

SUMMARY
A series of 102 patients with presumptive acute appendicitis entered a prospective, randomized, clinical trial of intrarectal metronidazole given over a 48-h period commencing before surgery. Adequate levels of circulating metronidazole were achieved. A significant reduction in the incidence of anaerobic wound infection was observed in the treated group ($P<0{\cdot}02$). The convenience and short duration of the prophylactic regimen allowed early discharge from hospital. No untoward effects were observed.

THE success of prophylactic metronidazole in controlling serious wound infection due to Gram-negative anaerobic organisms after elective colonic surgery has already been established (Goldring et al., 1975; Willis et al., 1977), although the importance of simultaneous administration of an antimicrobial agent to control organisms of the coliform group remains uncertain. In acute appendicitis, Willis et al. (1976) have extended this prophylactic antimicrobial approach to emergency surgery, using metronidazole alone over 8 days, commencing just before surgery.

The aim of the present study was to examine further this prophylactic approach and to assess the efficacy of short term metronidazole, given solely as suppositories, in preventing anaerobic wound infection after appendicectomy for acute appendicitis.

Patients and methods

A consecutive series of 102 patients in whom a presumptive diagnosis of acute appendicitis had been made entered the trial. Patients were randomly allocated to receive identically marked suppositories containing either metronidazole 1 g or placebo (Witepsol). The first suppository was inserted at the time of presumptive diagnosis and thereafter a further suppository was inserted 8-hourly for 2 days. Proctoscopy was performed within 24 h of completing the course in the first 41 patients in the series.

Blood metronidazole levels

A venous blood sample was taken at the time of induction of general anaesthesia to measure the circulating level of metronidazole and the time interval between insertion of the initial suppository and blood sampling was noted.

Bacteriology specimens

The following specimens were taken for culture at the time of surgery: (*a*) a swab of peritoneal fluid; (*b*) a swab from the serosal aspect of the appendix; (*c*) after removal of the appendix and wound closure, the appendix was opened in its distal third and a swab of luminal content taken. All swabs were immediately immersed in Stuart's transport medium for transfer to the laboratory. Cultures were incubated both aerobically and anaerobically with 10 per cent added carbon dioxide for at least 48 h. The following culture media were used: 6 per cent horse blood agar, 6 per cent horse blood agar incorporating gentamicin sulphate 15 μg/ml, MacConkey's agar and Robertson's cooked meat broth. Bacteria were identified by standard procedures (Cowan and Steel, 1974).

Pathology

In all cases the appendix was subjected to routine histopathological examination.

Wound inspection

Formal wound inspection was made on the third or fourth day and again on the tenth day; in all cases where early ward discharge had been allowed arrangements were made for wound inspection on the tenth postoperative day. For the purposes of this study 'wound infection' was defined as the presence of pus or a purulent exudate at the wound.

Exclusions

Twelve patients were withdrawn from the study, 4 because of an error in the diagnosis at operation (1 acute cholecystitis, 1 caecal diverticulitis, 1 inflamed Meckel's diverticulum and 1 already established appendix abscess). Six patients were excluded because they had received antibiotics (intra- or postoperatively); in 5 of these cases the surgeon had been unwilling to leave his patients in a double-blind situation and in the sixth case preoperative administration of an antibiotic before hospital admission was discovered. Two patients were excluded because they were given the wrong suppositories. Thus 90 patients remained in the study.

Results

Matching of the groups (*Table I*)

Comparison of the groups with regard to age and sex showed no significant differences. In this study we classified appendices as normal, inflamed or gangrenous/ruptured. Unlike the earlier study of Willis et al. (1976) we have not recognized lymphoid hyperplasia as a significant pathological entity and have included such appendices in our normal group. Eighty-four per cent of appendices in our series were significantly inflamed. While there was no significant difference between the incidence of inflamed and gangrenous/ruptured appendices in the placebo and metronidazole groups, there were significantly fewer normal appendices in the metronidazole group compared with the placebo group and in this respect there was a slight bias against the metronidazole group (*Table I*). The relative incidence of acute appendicitis in the under-13-year-olds is greater than our figures suggest since most younger children from our area are admitted to a paediatric hospital. The anatomical sites of the appendix at operation were similar in both groups.

Blood metronidazole levels at the time of surgery

For 36 of the 42 patients who received metronidazole, the time interval between insertion of the first suppository and induction of anaesthesia was recorded and this is plotted against the circulating level of metronidazole in *Fig*. 1. At commencement of surgery following the initial single suppository, the mean

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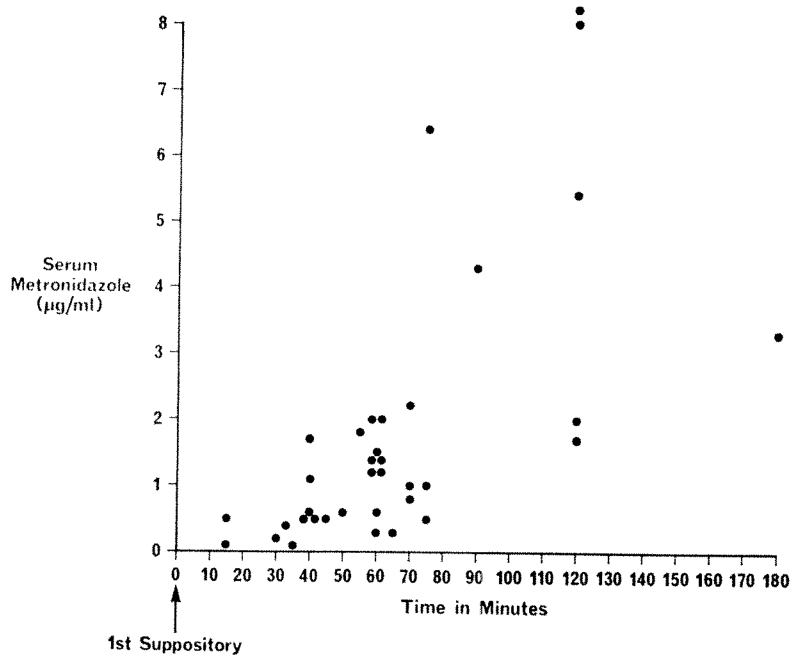

Fig. 1. Levels of circulating metronidazole at the time of surgery after a single 1-g suppository.

Table I: COMPARISON OF GROUPS

	Metronidazole (n = 42)	Placebo (n = 48)
Male/Female	27/15	27/21
Age		
<13	6	8
13–24	26	27
25–50	7	12
>50	3	1
Pathology		
Normal	2*	12*
Inflamed	30	31
Gangrenous ruptured	10	5

* There are significantly fewer normal appendices in the metronidazole group ($P<0{\cdot}0066$, Fisher's exact test). No other significant differences exist between the groups. The overall incidence of normal appendices in the series was 16 per cent; inflamed appendices 67 per cent; ruptured/gangrenous appendices 17 per cent.

Table II: BACTERIOLOGY

	Metronidazole		Placebo	
	Anaerobes		Anaerobes	
Site	Present	Absent	Present	Absent
Peritoneal fluid	2	40	2	46
Appendix serosa	10	32	13	35
Appendix lumen*	32	8	43	5
Operation wound	0	42	7	41

* Luminal swabs were not obtained in 2 patients.
In every case one or more strain of bacteroides comprised the anaerobic flora. Two instances of purely aerobic wound infection occurred (*see* text).

blood metronidazole level was 1·8 mg/l and the range was 0·1–8·2 mg/l. This indicated that satisfactory absorption from rectal mucosa was taking place, despite the short interval between insertion of the first suppository and sampling of blood. The mean time interval from insertion of the initial suppository to surgery was 64 min. From *Fig.* 1 it is evident that higher blood levels can be attained when this time is longer.

Bacteriology (*Table II*)
The presence of organisms in the peritoneal cavity, serosa of the appendix or indeed the lumen of the appendix gave little indication as to whether wound infection was likely to occur. Likewise, the presence or absence of turbid or clear peritioneal fluid was a poor guide to the development of an infected wound.

Wound infection
Seven of the 48 patients in the control group had severe anaerobic wound infection. In 5 of these patients a cellulitis developed which spread into the flank. In 3 this was associated with marked postoperative paralytic ileus and abscess formation requiring surgical drainage. In all 7 cases pus from the wound yielded bacteroides and in all instances the organisms were present in the lumen of the appendix. All 7 wounds yielded coexisting coliform organisms (*Escherichia coli* 6; *Klebsiella aerogenes* 1). Blood cultures were negative. All cases responded to a course of intramuscular gentamicin and lincomycin. The minimum inpatient stay was 18 days.

By contrast, there was no instance of anaerobic wound infection in the group that received metronidazole suppositories and this advantage for patients in the treated group is statistically significant ($P<0{\cdot}02$, Fisher's exact test).

There were 2 patients in the series who had aerobic wound infection, both in the metronidazole group. (One severe wound infection due to *Staphylococcus aureus* resulted in a 2½ week stay in hospital.) One of these cases was a patient who developed a stitch abscess on the tenth day having been discharged on the third postoperative day with an initially satisfactory wound. One millilitre of pus was aspirated from the wound and this yielded a non-haemolytic streptococcus.

The use of peritoneal drains

Twelve patients in the series had peritoneal drains brought out through a separate stab wound. The usual indication for drainage was the finding of purulent peritoneal exudate and/or a gangrenous or ruptured appendix. Of the 12 patients, 4 had received placebo (3 of whom developed wound infection) and 8 had received metronidazole (none developed infection).

Exclusions

Of the 12 patients excluded from the study, 5 were withdrawn from the trial by the surgeon at the time of operation after administration of the initial preoperative suppository (metronidazole, 2; placebo, 3). All 5 had ruptured appendices, all had separate stab wound drains and received parenteral gentamicin and lincomycin for at least 3 days. Wound infection occurred in 2 of these cases (placebo and metronidazole one each) and in both cases culture yielded coliforms and bacteroides.

Proctoscopy

Forty-one patients (19 placebo; 22 metronidazole) had proctoscopy performed after completing the course of suppositories. No patient showed any abnormality. No practical difficulties arose in the administration of suppositories in the early postoperative period.

Discussion

This study of emergency appendicectomies clearly shows the ability of metronidazole to prevent wound infection from endogenous anaerobic bowel microflora. Use of the intrarectal route to administer the drug is safe and convenient and has clear advantages in the preoperative and immediate postoperative situation where the oral route is not always feasible and where intravenous administration would be unnecessary. Our results confirm that metronidazole is rapidly and satisfactorily absorbed via the rectal mucosa and that therapeutic blood levels can be attained even when there is only a short time interval between insertion of the first suppository and commencement of the operation. Willis et al. (1976) have had similar success using metronidazole suppositories as part of an 8-day course of therapy. In the light of our results, this longer course involving postoperative oral administration would appear to be unnecessary provided that the patient receives protective antimicrobial therapy during the peroperative period, i.e. the period during which surgery is exposing tissues to contamination from endogenous bowel flora. One further practical advantage of a short 2-day course of metronidazole is that it does not interfere with early hospital discharge around the third or fourth postoperative day.

Since there has been no significant evidence for strict anaerobes developing resistance to metronidazole over many years of widespread and varied use, a short course of the drug seems unlikely to precipitate the emergence of bacterial resistance.

Acknowledgements

We wish to thank all members of the Surgical Division of the Victoria Infirmary, Glasgow, for allowing us to study their patients for this trial.

We are also indebted to Miss I. K. Morton, Principal Pharmacist, and the ward nursing staffs for their efficient help in randomizing the allocation of patients to the trial.

Suppositories were kindly supplied by Messrs May & Baker Ltd, Dagenham, Essex, who also carried out estimation of serum metronidazole levels.

References

COWAN S. T. (1974) *Cowan and Steel's Manual for the Identification of Medical Bacteria.* London, Cambridge University Press.

GOLDRING J., SCOTT A., MCNAUGHT W. et al. (1975) Prophylactic oral antimicrobial agents in elective colonic surgery. *Lancet* **2**, 997–999.

WILLIS A. T., FERGUSON I. R., JONES P. H. et al. (1976) Metronidazole in prevention and treatment of bacteroides infections after appendicectomy. *Br. Med. J.* **1**, 318–320.

WILLIS A. T., FERGUSON I. R., JONES P. H. et al. (1977) Metronidazole in prevention and treatment of bacteroides infections in elective colonic surgery. *Br. Med. J.* **1**, 607–609.

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A double-blind trial of a single intravenous dose of metronidazole as prophylaxis against wound infection following appendicectomy

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SUMMARY

One hundred patients undergoing appendicectomy through a right iliac fossa incision were randomized to receive normal saline or 500 mg metronidazole as an intravenous infusion during the operation. One patient in the saline group developed an erythematous rash. There were 13 wound infections (as defined by the discharge of pus), 12 (out of 51) in the saline group and 1 (out of 49) in the metronidazole group. Bacteroides *spp. were frequently cultured from the lumen of removed appendices and from pus obtained from infected wounds. This work supports the value of metronidazole but suggests that a single-dose regimen is adequate for prophylaxis.*

AFTER appendicectomy a high proportion of infected wounds has yielded *Bacteroides* spp. (Leigh et al., 1974) and a previous study (Willis et al., 1976) has shown that a regimen of metronidazole suppositories and subsequently tablets given for a period of 1 week significantly reduced the incidence of wound infection.

We felt that the use of suppositories held certain disadvantages, and that treatment for 7 days might be unnecessary. Metronidazole administered as an intravenous infusion has been found safe and effective in the treatment of anaerobic infections (Selkon et al., 1977), and a single 500-mg dose infused over 20 min produced a mean rise of 11·7 μg/ml 30 min after administration had ceased in 14 patients (Eykyn and Phillips, 1977). As these serum levels appeared to compare favourably with those achieved by treatment with metronidazole suppositories (Houghton and Templeton, 1978), we have investigated the efficacy of a single intravenous dose of 500 mg of metronidazole administered during appendicectomy as prophylaxis against wound infection.

Patients and methods

Patients who underwent appendicectomy via a right iliac fossa approach in the General Infirmary at Leeds during two periods of time between July 1977 and April 1978 were included in the study. A total of 116 patients aged between 5 and 73 years was included but 16 were rejected before the code was broken (Meckel's diverticulitis, 1; administration of additional antibiotics, 4; data mislaid, 3; failure to administer the infusion or adhere to the protocol, 8). The study was carried out using a randomized, double-blind technique. Identical infusion bottles containing 500 mg metronidazole in 100 ml saline or 100 ml physiological saline were stored in numbered sequence in the operating theatre. When a patient was taken to theatre for appendicectomy the numbered bottle was given to the anaesthetist who commenced the infusion once the anaesthetic had been induced and allowed the 100 ml to run in over approximately 10 min. At the end of the procedure data were recorded by the surgeon on a similarly numbered card. The wound was examined daily by the surgeon whilst the patient was in hospital and also at the first visit to the outpatient department. An infection was defined as the discharge of pus from the wound.

A swab was taken from the lumen of the appendix and also from all wound infections which appeared during inpatient stay. All the lumen swabs but only about half the wound swabs were placed immediately into Robertson's meat broth and plated out within 30 min. The Robertson's meat broth was subcultured at 24 h. The aerobic media used for inoculation and subculture were blood agar and MacConkey agar and the anaerobic pre-reduced media used were blood agar, neomycin blood agar and kanamycin (100 μg/ml) and vancomycin (7·5 μg/ml) blood agar. The wound swabs not transported in Robertson's meat broth were inoculated directly on to these media. The time between taking the swab and inoculation of the media was variable, but on occasions it was in excess of 4 h. Bacteria were identified by standard methods. Anaerobic Gram-negative bacilli were designated *Bacteroides* spp.

The code was broken when 100 patients had satisfactorily completed the trial.

Results

Fifty-one patients received saline and 49 metronidazole. The two groups were well matched except with respect to the frequency of wound drainage (*Table I*), which was more commonly employed in the control group.

Pus producing wound infection was seen in 1 wound from the metronidazole group (2 per cent) and in 12 from the saline control group (24 per cent). This difference was significant at $P = 0{\cdot}002$ using Fisher's exact test. Reddening of the wound, which settled without additional treatment and did not result in a discharge of pus, was seen in a further 4 wounds, 2 in the metronidazole group and 2 in the control group.

The prevalence of various species of bacteria recovered from the appendix lumina and from the pus of the infected patients is shown in *Tables II* and *III*. All infected wounds discharged pus between 3 and 14 days after appendicectomy.

The patient who was treated with metronidazole and developed an infected wound did not have a drain but 3 of the patients in the saline group who became infected did have wound drains.

Discussion

A wound infection resulting in the production of pus was found in 12 of the 51 patients who received prophylaxis with intravenous saline. This infection rate of 24 per cent is similar to rates reported in other recent series in which no antibiotic prophylaxis was employed (Rickett and Jackson, 1969; Benson et al., 1973; Bates et al., 1974).

Leigh et al. (1974) recovered *Bacteroides* spp. from 90 per cent of infected wounds after appendicectomy. Our overall recovery rate of 40 per cent was due to our failure to isolate *Bacteroides* spp. from dry swabs, but the rate was 80 per cent from the swabs sent in

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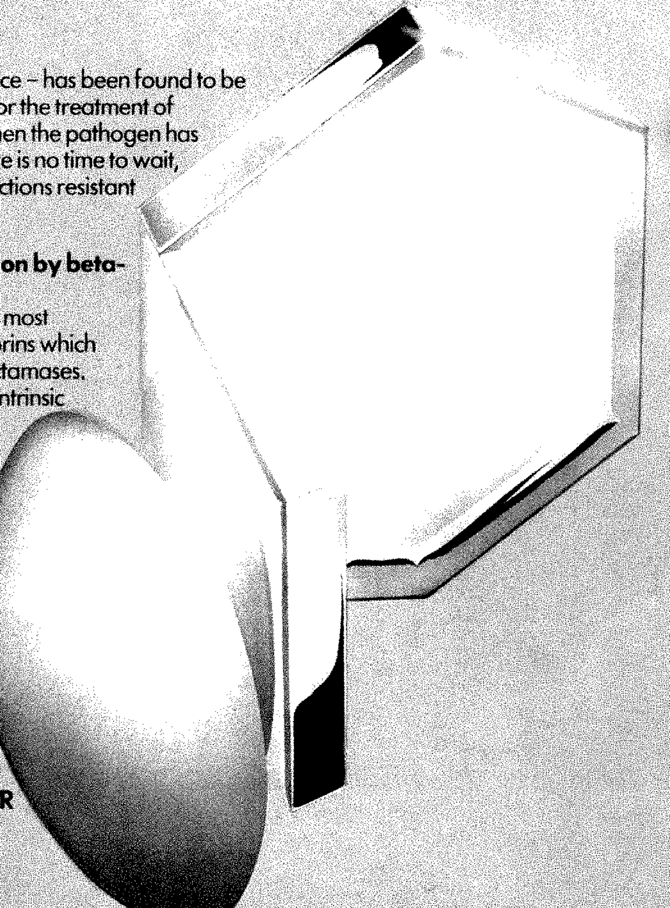

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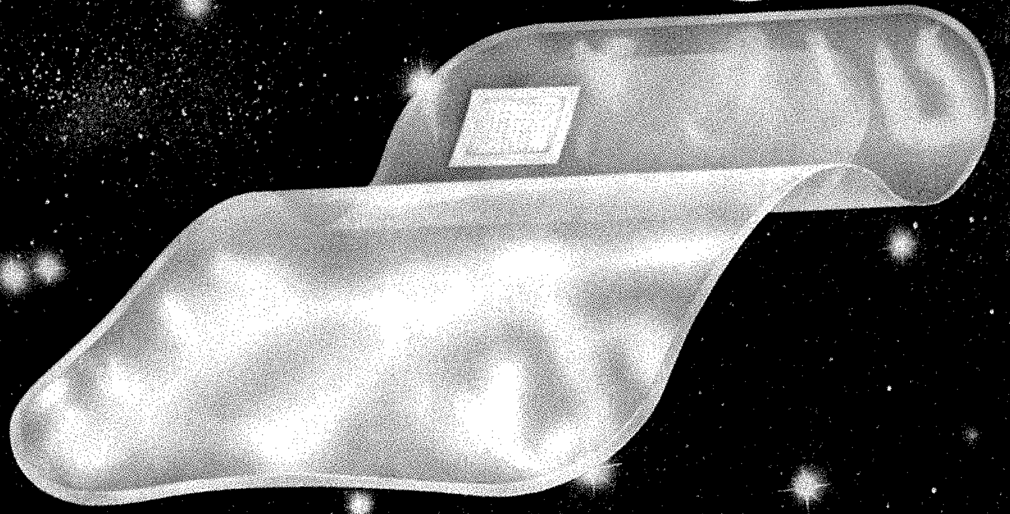

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Table I: DATA FROM 49 PATIENTS WHO RECEIVED INTRAVENOUS METRONIDAZOLE AND 51 WHO RECEIVED SALINE DURING APPENDICECTOMY

	Metronidazole	Control
Age (yr±s.d.)	22±15	22±14
Male/female	25/24	26/25
Appendix		
Normal	9	11
Inflamed	27	25
Gangrenous	7	9
Local pus collection	4	4
Peritonitis	2	2
Drains	5	9
Infected wounds	1	12

Table II: PERCENTAGE FREQUENCY DISTRIBUTION OF BACTERIAL SPECIES RECOVERED FROM THE LUMEN OF REMOVED APPENDICES AND FROM THE WOUND PUS IN THE SALINE GROUP

Organism	Appendix lumen ($n=11$)	% in lumina	Wound pus ($n=10$)	% in wound pus
Coliform spp.	11	100	8	80
Bacteroides spp.	6	55	4	40
Enterococci	2	18		
Clostridium spp.	2	18	1	10
Diphtheroid	1	9		
Bacillus spp.	1	9		
Lactobacillus spp.	1	9	1	10
Staphylococcus aureus	1	9		
Haemophilus influenzae	1	9		
Pseudomonas aeruginosa			1	10

A bacteriological specimen was not obtained from 2 infections which discharged pus subsequent to the patients' discharge from hospital.

Table III: BACTERIAL SPECIES RECOVERED FROM THE LUMEN OF THE REMOVED APPENDIX AND FROM THE WOUND PUS IN THE SINGLE PATIENT WHO RECEIVED METRONIDAZOLE AND DEVELOPED INFECTION

Organism	Appendix lumen ($n=1$)	Wound pus ($n=1$)
Bacteroides spp.	Yes	—
Coliform spp.	Yes	Yes
Clostridium spp.	Yes	—
Diphtheroid	Yes	—

Robertson's meat broth. This organism is clearly important in wound infections following appendicectomy. Nevertheless, we cultured a total of four other organisms from the wounds of patients who had not received metronidazole. Although the effectiveness of metronidazole as an agent for use against *Bacteroides* is now well established (Whelan and Hale, 1973; Willis et al., 1974, 1976, 1977), most of the remaining organisms isolated here do not lie within its spectrum of activity. There is evidence, however, that obligate anaerobes such as *Bacteroides fragilis* may inhibit phagocytosis (Ingham et al., 1977) and thereby allow other organisms to multiply. Such a mechanism might explain the effectiveness of metronidazole in reducing the incidence of infections involving a wide spectrum of organisms.

In this trial we have found that a single intravenous injection of metronidazole produced a reduction in the incidence of infection similar to that achieved by a combined suppository and tablet regimen lasting 7 days. Although Willis et al. (1976) 'considered it inappropriate, however, to use the intravenous route for evaluating the drug as a prophylactic agent', we feel that it has certain advantages in routine practice.

The value of antibiotics for the prevention of wound infection after appendicectomy is at present rather unclear. Although some reports claim marked benefit from their use (Rickett and Jackson, 1969; Longland et al., 1971; Bates et al., 1974), this impression has not been universal (Magarey et al., 1971). There is at least agreement between reports upon the value of metronidazole, although no trial has yet set out to compare this drug with an antibiotic.

We conclude that a single intravenous dose of metronidazole administered at the time of appendicectomy is a convenient, safe, cheap and effective method of reducing wound sepsis rates.

Acknowledgements

We would like to thank Mr E. A. Benson, Mr R. L. Doig, Mr G. L. Hill, Professor D. Johnston, Mr J. H. Shoesmith and Mr F. G. Smiddy for permission to carry out this trial upon patients admitted under their care. We thank the anaesthetic and theatre staff of the General Infirmary at Leeds for their cooperation, and Dr J. Collier and Miss E. M. Colhoun of May and Baker Ltd for the supplies of metronidazole and placebo and for their help with the organization of the trial.

References

BATES T., DOWN R. H. L., HOUGHTON M. C. V. et al. (1974) Topical ampicillin in the prevention of wound infection after appendicectomy. *Br. J. Surg.* **61**, 489–492.

BENSON E. A., BROWN G. J. A. and WHITTAKER M. (1973) Prevention of wound infection in acute appendicitis. *Lancet* **2**, 322.

EYKYN S. and PHILLIPS I. (1977) Intravenous metronidazole in the treatment of anaerobic sepsis. *Excerpta Med. Int. Congr. Ser.* 438, p. 393.

HOUGHTON G. W. and TEMPLETON R. (1978) Statistical analysis of serum metronidazole levels in patients receiving the drug mainly by suppository. *J. Antimicrob. Chem.* **4**, Suppl C, pp. 91–96.

INGHAM H. R., SISSON P. R., THARAGONNET D. et al. (1977) Inhibition of phagocytosis in vitro by obligate anaerobes. *Lancet* **2**, 1252–1254.

LEIGH D. A., SIMMONS K. and NORMAN E. (1974) Bacterial flora of the appendix fossa in appendicitis and postoperative wound infection. *J. Clin. Pathol.* **27**, 997–1000.

LONGLAND C. J., GRAY J. G., LEES W. et al. (1971) The prevention of infection in appendicectomy wounds. *Br. J. Surg.* **58**, 117–119.

MAGAREY C. J., CHANT A. D. B., RICKFORD C. R. K. et al. (1971) Peritoneal drainage and systemic antibiotics after appendicectomy. *Lancet* **2**, 179–182.

RICKETT J. W. S. and JACKSON B. T. (1969) Topical ampicillin in the appendicectomy wound. *Br. Med. J.* **4**, 206–207.

SELKON J. B., INGHAM H. R. and HALE J. H. (1977) Experience with intravenous administration of metronidazole in man. *Excerpta Med. Int. Congr. Ser.* 438, p. 390.

WHELAN J. P. F. and HALE J. H. (1973) Bactericidal activity of metronidazole against Bacteroides fragilis. *J. Clin. Pathol.* **26**, 393–395.

WILLIS A. T., BULLEN C. L., FERGUSON I. R. et al. (1974) Metronidazole in the prevention and treatment of bacteroides infections in gynaecological patients. *Lancet* **2**, 1540–1543.

WILLIS A. T., FERGUSON I. R., JONES P. H. et al. (1976) Metronidazole in prevention and treatment of bacteroides infections after appendicectomy. *Br. Med. J.* **1**, 318–321.

WILLIS A. T., FERGUSON I. R., JONES P. H. et al. (1977). Metronidazole in prevention and treatment of bacteroides infections in elective colonic surgery. *Br. Med. J.* **1**, 607–610.

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Short term metronidazole therapy contrasted with povidone-iodine spray in the prevention of wound infection after appendicectomy

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SUMMARY

In a prospective, randomized trial metronidazole was found to be significantly better than povidone-iodine in reducing the incidence of wound infection after appendicectomy ($P<0{\cdot}005$). The metronidazole was given as a 3-day course and was found to be as effective as the established 7-day course. Over 65 per cent of the wound infections presented after the patients had been discharged from hospital.

WOUND infection is a common complication of appendicectomy (*Lancet*, 1970, 1971) increasing both the morbidity and the length of stay in hospital. Previous work in this hospital (Gilmore and Martin, 1974) has shown that povidone-iodine sprayed into the incision during closure reduces wound infection from 16 to 8 per cent. More recently the use of metronidazole (Willis et al., 1976) has shown a reduction in the wound infection rate from 22 to 10 per cent.

We report here the results of a prospective trial comparing short term (3 days) metronidazole administration with povidone-iodine spray for the prevention of wound infection.

Patients and methods

All the patients admitted to the Royal Berkshire and Battle Hospitals for emergency appendicectomy were randomly allocated to one of the treatment groups. Group 1 received a metronidazole 1-g suppository 2 h before operation and every 8 h after operation for a total of 3 days. If the oral form could be tolerated postoperatively 200 mg every 8 h was administered instead of the suppository. Children under 10 received 0·5-g suppositories. Group 2 received povidone-iodine dry powder into the wound after closure of the peritoneum, sprayed from a distance of 20 cm for approximately 8 s, so that a good coating of powder was visible in and around the wound. A further dose was applied after closure of the skin.

A standard appendicectomy technique was performed by all the surgeons involved. Wounds were inspected by an independent observer postoperatively, and the patients were reviewed at a special follow-up clinic between 3 and 5 weeks after leaving hospital. Patients were also asked to attend the ward should any discharge from the wound occur during this period.

A wound infection was defined as any purulent or infected sero-sanguineous discharge from the wound.

Results

One hundred and twenty-nine patients were entered in the trial in a 3-month period. Four patients were withdrawn from the trial. Two had received systemic antibiotic prophylaxis for suspected rheumatic heart disease, a third had an incomplete course of metronidazole and the fourth had systemic antibiotics for pneumonia. None of these patients developed a wound infection. A further 15 patients failed to attend the follow-up clinic but did reply to a postal inquiry and have been included in the trial.

There were 65 patients in the metronidazole group and 60 in the povidone-iodine group. Both groups matched for age and sex. Wound infection occurred in 4 patients in the metronidazole group (6·2 per cent), which was significantly less than in the povidone-iodine group in which there were 16 patients with infection (26·6 per cent) ($P<0{\cdot}005$—using χ^2 with Yates' correction). Eight of these infections (2 metronidazole, 6 povidone) were superficial and had healed within 2 or 3 days. The infection rate in relation to the severity of the appendicitis is shown in *Table I*.

The average length of stay in hospital was 4·9 days in the non-infected patients but 8·6 days in those infected. Thirteen of the wound infections presented after discharge from hospital and 3 of these patients (all in the povidone group) required readmission. Culture swabs of the wound infections were only available in 9 cases—7 of which showed growth with bacteroides organisms (all in the povidone group).

Table I: INFECTION RATE RELATED TO SEVERITY OF APPENDICITIS

	Metronidazole		Povidone-iodine	
Severity	No.	Infected	No.	Infected
Normal	14	0	12	1
Acutely inflamed	41	1	34	8
Gangrenous	5	1	7	2
Perforated	5	2	7	5
Total	65	4	60	16

Discussion

Because of good back-up facilities provided by the local family practitioners, we are able to send many of our patients home earlier after operation than is usually advocated (*Lancet*, 1970). For this reason nearly two-thirds of the wound discharges occurred after the patients had left hospital.

The patients were asked to attend the ward should they develop any complication with their wound, so that culture swabs could be taken. However, several did not attend and the diagnosis of wound infection was made retrospectively at the special follow-up clinic and included any wound discharge, however minor. These minor discharges, possibly due to iodine irritation, may explain the high rate of wound infection in the povidone-iodine group and it is a pity that for ethical reasons based on previous reports (Gilmore and Martin, 1974; Willis et al., 1976) a control group was not included in the design of our trial. Even if these minor wound discharges are excluded, metronidazole is still significantly better than povidone-iodine ($P = 0{\cdot}02$).

Unfortunately as many patients did not attend for bacterial culture swabs to be taken, conclusions regarding the bacteriology cannot be made, but it is

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interesting to note that in the povidone group at least 7 of the 16 wound infections grew bacteroides and in 4 this was in pure culture.

Although the numbers in our trial were smaller, we were unable to reproduce the previous results obtained from our hospital by Gilmore and Martin (1974) using povidone-iodine. This was surprising since there had been little change in the proportion of severe cases, in the age and sex distribution, and no alteration in the composition of the povidone-iodine spray. If the minor wound discharges are excluded there was still a wound infection rate of 16 per cent which was similar to the control group in the previous study. However, at the time of the previous study, anaerobic culture techniques for bacteroides organisms were not as stringent as at present and perhaps some wound discharges were considered sterile and therefore not considered a wound infection. McClusky (1976) found that povidone-iodine solution did not prevent wound infection after general surgical operations and Galland et al. (1977) drew similar conclusions using povidone-iodine spray.

The incidence of wound infection after appendicectomy for a gangrenous or perforated appendicitis is extremely high. Three of the 4 cases of wound infection in the metronidazole group occurred in such cases. It would seem, therefore, that although metronidazole is fairly effective in reducing the incidence of wound infection, further measures such as delayed primary suture or additional prophylactic antibiotics should be considered in cases of gangrenous or perforated appendicitis.

We have found a 3-day course of metronidazole to be equally effective as the previously described 7-day course (Willis et al., 1976). Animal experiments (Burke, 1961) suggest that systemic antibiotics given before or within 3 h of bacterial inoculation of a wound will suppress bacterial infection of that wound. Since most infections after appendicectomy are due to endogenous bacterial contamination it will be interesting to see if a two-dose course of metronidazole will also be effective in reducing wound infection.

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References

BURKE J. F. (1961) The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery* 50, 161–168.

GALLAND R. B., SAUNDERS J. H., MOSLEY J. G. et al. (1977) Prevention of wound infection in abdominal operations by pre-operative antibiotics or povidone-iodine. *Lancet* 2, 1043–1045.

GILMORE O. J. A. and MARTIN T. D. M. (1974) Aetiology and prevention of wound infection in appendicectomy. *Br. J. Surg.* 61, 281–287.

LANCET (1970) Wound infection after appendicectomy. 1, 930–931.

LANCET (1971) Sepsis after appendicectomy. 2, 195.

MCCLUSKY B. (1976) A prospective trial of povidone iodine solution in the prevention of wound sepsis. *Aust. NZ J. Surg.* 46, 254–256.

WILLIS A. T., FERGUSON I. R., JONES P. H. et al. (1976) Metronidazole in prevention and treatment of bacteroides infections after appendicectomy. *Br. Med. J.* 1, 318–321.

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Left renal vein ligation in surgery for abdominal aortic aneurysm

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OCCASIONALLY, during surgery on the abdominal aorta, division of the left renal vein is required for technical reasons. In this paper we present 6 patients with abdominal aortic aneurysms in whom the left renal vein was divided but not reconstituted. There were no deaths and all 6, now between 6 months and 3 years after operation, show no significant disturbance of renal function.

Patients and methods

All 6 patients (4 males and 2 females) had abdominal aortic aneurysms. Four were elective cases, one aneurysm was expanding and required urgent operation and the other was ruptured.

In most cases division of the left renal vein was required to obtain safe control of the aorta above the neck of the aneurysm or because the vein was densely adherent to the aorta. In one a retro-aortic vein was accidentally torn. In all cases the vein was divided well to the right so as to avoid the left adrenal vein, the most medial tributary.

Blood urea estimations were carried out preoperatively on all patients and serum creatinine was measured in 2 of the 4 elective cases. Postoperative investigations were performed within 6 months of leaving hospital and included blood urea and serum creatinine estimations and an intravenous pyelogram. It can be seen from *Table I* that all patients maintained satisfactory renal function and those with blood urea and creatinine levels close to the upper limit of normal have normal intravenous pyelograms. Of particular interest is the observation that all 6 patients have a normal blood pressure.

Table I: DETAILS OF THE SERIES AND POSTOPERATIVE RENAL FUNCTION TESTS

Case	Age (yr)	Sex	Operation	Blood pressure (mm Hg) Preop.	Blood pressure (mm Hg) Postop.	Blood urea (mmol/l) Preop.	Blood urea (mmol/l) Postop.	Serum creatinine (mmol/l) Preop.	Serum creatinine (mmol/l) Postop.	IVP
T. W.	42	M	Elective	150/100	140/80	4·1	4·2	57	56	Normal
W. M.	70	M	Urgent	150/100	140/80	13·3	8·9	—	181	Normal
L. H.	75	F	Elective	200/105	160/90	6·2	8·2	—	90	Normal
T. H. W.	72	M	Ruptured	80/52	110/70	35·0	8·3	—	120	Normal
T. S.	72	M	Elective	180/95	180/100	5·3	4·8	64	80	Normal
J. N.	58	F	Elective	170/110	160/95	6·2	7·0	—	105	Normal

Discussion

The major tributaries of the left renal vein are the gonadal veins and the left adrenal vein. The left inferior phrenic vein usually joins the left adrenal vein but may drain directly into the left renal vein. The gonadal vein anastomoses with the lumbar veins and capsular veins drain into the lumbar system. De Laurentis and Iyenager (1970) demonstrated these and other collateral veins draining the kidney after left renal vein ligation using an ingenious radiological technique cannulating a vein in the pampiniform plexus. Szilagyi et al. (1969) reported 20 patients in whom they temporarily divided and reconstituted the left renal vein with no harm to the patients. Neal and Shearburn (1967) reported 11 patients in whom the left renal vein was permanently transected. There were 3 deaths in their series but no death was attributable to left renal vein ligation. Simon et al. (1972) reported 13 patients in whom the left renal vein or a major tributary was divided to allow end-to-end anastomosis in splenorenal shunts for portal hypertension. There were 5 deaths due to liver disease. None of these patients had any impairment of renal function and the 8 survivors all had normal intravenous pyelograms and renal function tests. Only one example of major damage to the kidney has been found in a review of the literature; Royster et al. (1974) have reported one patient with a ruptured aneurysm who died several days after operation and in whom post-mortem examination revealed venous infarction of the left kidney following left renal vein ligation.

Conclusion

Left renal vein ligation is a safe procedure. There are adequate collateral channels into which venous return from the left kidney can drain, and, provided that the left renal vein is divided far enough to the right to preserve the adrenal and gonadal veins, no harm should come to the left kidney.

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References

DE LAURENTIS D. A. and IYENAGER S. R. K. (1970) Renal function and a technique for venography after left renal vein ligation. *Am. J. Surg.* **120**, 41–45.

NEAL H. S. and SHEARBURN E. W. (1967) Division of the left renal vein as an adjunct to resection of abdominal aortic aneurysms. *Am. J. Surg.* 113, 763–765.

ROYSTER T. S., LACEY L. and MARKS R. A. (1974) Abdominal aortic surgery and the left renal vein. *Am. J. Surg.* **127**, 552–554.

SIMON J. S., BROWN A. A. and ROSS H. B. (1972) Ligation of the left renal vein in splenorenal anastomosis without impairment of renal function. *Br. J. Surg.* **59**, 170–173.

SZILAGYI D. E., SMITH R. F. and ELLIOTT J. P. (1969) Temporary transection of the left renal vein: a technical aid. *Surgery* **65**, 32–40.

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The morbidity of carotid endarterectomy

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SUMMARY

The results of 72 carotid endarterectomy operations carried out by three consultant surgeons were analysed. Thirty-eight operations (32·8 per cent) were performed in patients with mild or resolving stroke and 33 operations (45·9 per cent) in patients with transient ischaemic attacks and/or amaurosis fugax. Five patients (7 per cent) died in the early postoperative period, 2 as a result of strokes and the others from cardiac causes. Seventy-six per cent of patients had a satisfactory long term result, remaining free from stroke, blindness or recurrent transient ischaemic attacks over the follow-up period of 1–7 years.

There were 10 patients (13·8 per cent), including 2 who died, who developed early postoperative neurological deficits; 4 (5·5 per cent) had transient defects and 6 (8·3 per cent) had permanent deficits. Of these patients, 4 had proved occlusions of the reconstructed artery. In 3 patients, cerebral embolization during operation was suspected as the cause. There were, in addition, 2 asymptomatic patients whose reconstruction was shown to be occluded on follow-up postoperative angiography. The continued absence of symptoms, therefore, is no guarantee that the reconstruction is patent and some more objective method of assessment is necessary if the results of carotid endarterectomy are to be critically analysed. The incidence of neurological deficits could, it is believed, be reduced by greater experience with the operation, the routine use of peroperative intra-arterial shunting and peroperative angiography to confirm the patency of the reconstruction.

CEREBROVASCULAR accidents—strokes—are a common cause of death and serious disablement. The incidence in Ireland is 200 per 100 000 population and in Britain it is 185 per 100 000 population; 34·9 per cent of the patients die within 3 weeks of onset of the stroke and 54·1 per cent die within 1 year (Radic et al., 1977). Stroke is, therefore, a major health problem and little progress has been made in its management. Prevention remains a worth-while goal.

Forty per cent of patients with stroke have the principal vascular occlusion confined to the extracranial vasculature and indeed 75 per cent of patients with ischaemic stroke have at least one obstructive lesion at a surgically accessible site (Fisher, 1951; Engell, 1973). Medical management of the carotid lesion based on the prevention of thrombotic occlusion of the internal carotid or distal embolism is still controversial. The efficacy of either anticoagulants or antiplatelet agents in reducing the mortality from stroke has not yet been proved.

Studies have shown the superiority of surgical over medical management of the extracranial vessel lesions (Bauer et al., 1969; Fields et al., 1970). These studies and other reports, most notably those of Javid et al. (1974) and Thompson and Talkington (1976), confirm the value of surgical management of internal carotid disease both in the reduction of transient ischaemic attacks and the prevention of death from stroke. The purpose of this retrospective study is to review our experience with the operation of carotid endarterectomy for internal carotid artery disease, to analyse the complications of the operation and to determine the effectiveness of the procedure.

Patients and methods

The records of 64 patients who had a carotid endarterectomy operation in St Laurence's Hospital, Dublin, during the period 1970–7 were reviewed. Seventy-two operations were carried out on the internal carotid artery. The operations were performed by the three consultants on the surgical professorial unit. In 56 patients the operation was unilateral and in 8 patients bilateral operations with a suitable interval between them were performed. The age range was 42–72 years. There were 17 females and 47 males.

Clinical features

The presenting clinical features (*Table I*) were those classically associated with this disease; transient hemispheric attacks, amaurosis fugax and neck bruits. One patient presented with a palpable lump in the neck caused by the atheromatous deposit in the vessel. In only one patient was the neck bruit asymptomatic. Twenty-four of the patients had associated systemic hypertension.

Table I: CLINICAL FEATURES IN PATIENTS UNDERGOING CAROTID ENDARTERECTOMY

Mild or resolving stroke	38
Transient ischaemic attack	30
Amaurosis fugax	29
Neck bruit	24
Hypertension	24
Dysphasia	13
Headache	8
Completed stroke	4
Palpable mass in neck	1

Angiographic pattern of the disease

The disease was unilateral in 37 patients and bilateral in 27. The atheromatous lesion was an ulcerating plaque in 22 and a stenosing lesion in 53. The contralateral carotid was totally occluded in 3 patients. Only one patient had a totally occluded internal carotid artery operated on (*see* below).

Indications for operation

It is the practice of this unit to operate on patients with symptomatic, angiographically significant lesions of the internal carotid artery, either stenosis or an ulcerating plaque. Operation was rarely performed for advancing stroke or for patients with recently occluded vessels. Indeed, only one patient was operated on for advancing stroke with a recently occluded internal carotid artery. In 38 of 72 operations the indication was mild or resolving stroke. The remaining operations were performed for patients with either transient ischaemic attacks and/or amaurosis fugax.

Investigations

All patients were assessed by a neurologist and then subjected to the definitive diagnostic investigation—carotid angiography. Bilateral biplane carotid angiography with careful cerebral cross-flow studies was performed in the majority of patients. Four-vessel angiography was reserved for those patients with symptoms of vertebral–basilar disease, significant differences

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in upper limb pulsations or blood pressure and basal neck bruits.

Operation

The operation was performed under a general anaesthetic using halothane. An intra-arterial pressure transducer was inserted into a radial artery to monitor the arterial blood pressure and the blood pressure was maintained at optimum levels during the operation. Cerebral activity was monitored continually by an electroencephalogram (EEG). The carotid vessels were exposed through an oblique incision along the anterior border of the sternomastoid. The hypoglossal and vagus nerves were carefully identified. Internal carotid artery stump pressures were usually measured but were not regarded as the determinant for intraluminal shunting. An intraluminal shunt was used prophylactically when there was either significant contralateral disease or poor cerebral cross-circulation. Therapeutic shunting was employed if the EEG showed evidence of cerebral ischaemia during the operation. Heparin, 5000 units, was given intravenously just before clamping the carotid vessels. A standard open thrombo-endarterectomy was performed, usually closing the defect by a vein patch.

A peroperative angiogram was performed routinely over the last 2 years of the study.

Postoperative management

The presence of a new neurological deficit or the worsening of a previous defect was assessed as soon as the patient was conscious. The wound was drained for 48 h and heparin (5000 units every 8 h) was given subcutaneously for 24-48 h. An antiplatelet agent was then used, such as aspirin or dipyridamole, for 6 weeks. Hypertension was controlled if necessary.

Results

Mortality

There were 5 postoperative deaths—a 7 per cent mortality. Two patients died within 48 h of surgery from myocardial infarction. One patient was successfully resuscitated from an intraoperative cardiac arrest only to die 2 h later as a result of massive haemorrhage from a peptic ulcer. The reconstructed vessels were patent at autopsy in all 3 cases. The other 2 patients died from cerebrovascular accidents and they are discussed in more detail below.

Morbidity

Local complications: One patient had a permanent small visual defect after operation, presumably from embolism to a retinal vessel. Three patients developed a haematoma in the neck which required evacuation. Nine patients had transient injuries to the nerves close to the operative field. There were 6 patients with transient hypoglossal nerve palsies. Two patients had transient lesions of the mandibular branch of the facial nerve and 1 patient had evidence of damage to the superior laryngeal branch of the vagus nerve. Nearly all these patients had an uneventful recovery from the nerve damage but 3 of the patients with the XIIth nerve damaged still showed a neurological defect some months after the operation.

Neurological complications: Ten patients (13·8 per cent), including 2 who died, developed major neurological deficits postoperatively. These deficits manifested clinically as hemiplegia in 6 previously neurologically intact patients and as a significant worsening of a neurological problem in 4. In 8 patients the problem was first noted on the day of operation. Two patients developed signs on the second and third postoperative days.

There were 6 permanent deficits (8·3 per cent): 2 patients died, 2 failed to show any resolution and 2 were left with a residual mild weakness of the hand. There were 4 transient neurological deficits (5·5 per cent) which cleared completely.

In these 10 patients the reconstructed artery was shown to be occluded in 4 at autopsy or on postoperative arteriogram; in 1 patient, acute thrombotic occlusion of the internal carotid artery distal to a stenosis was found at operation; in another, a wound haematoma probably caused compression of the internal carotid artery. The cause of the stroke in the remaining 4 patients could not be established unequivocally, but in 3 the operative and clinical findings favoured a diagnosis of cerebral embolism.

In none of the 10 patients was an abnormality detected on the peroperative EEG recordings. In only 2 of the patients was a shunt inserted and neither developed a permanent deficit. Seven of the remaining 8 patients met our criteria for shunting but were not shunted.

Follow-up

Of the 64 patients, 2 were not traced and 5 died in hospital, leaving 57 patients for review. The minimum follow-up period was 1 year and the longest, 7 years. Forty-nine patients (76 per cent) had a satisfactory outcome with freedom from further transient ischaemic attacks or strokes. There were 4 deaths, 1 from a lung tumour, 1 from a brain tumour and 2 from strokes. One of these strokes was an early postoperative complication, the patient dying some months later. A second patient died at 2 years of an ipsilateral cerebrovascular accident.

Two patients developed non-fatal strokes, one at 2 years and the other at 5 years postoperatively. In neither was the reconstructed artery implicated; in one an ipsilateral angiogram showed a patent reconstruction and in the other the opposite carotid territory was involved but angiography was not performed. Two patients had transient ischaemic attacks; in both the reconstructed vessel was patent on angiography.

Patency of reconstruction: Postoperative angiography was performed in 13 patients: in 9 the reconstruction was patent and satisfactory and in 4 the internal carotid artery was occluded. Two of these 4 patients were asymptomatic and the findings were unexpected.

There were 8 proved early occlusions of the endarterectomized carotid artery demonstrated by angiography or at reoperation or autopsy—an incidence of 11 per cent.

Discussion

The long term results of carotid endarterectomy in this and other series are satisfactory (*Table II*). Nearly 80 per cent of patients remain free from stroke, transient ischaemic attacks, transient or permanent blindness. The operation has a significant mortality and morbidity. The 7 per cent mortality rate in this series is similar to that found by others (*Table II*). Three of 5 patients died directly or indirectly from cardiac causes. The incidence of mortality is influenced by the clinical severity of the carotid disease, associated ischaemic heart disease and the experience of the surgical team.

The morbidity associated with carotid endarterectomy is either of local or of neurological origin. The local complications are usually more annoying than serious, although wound haematoma can compress the internal carotid artery with serious consequences, as occurred in 1 of our patients. Lesions of the VIIth, Xth and XIIth nerves are embarrassing not only to the patient but also to the surgeon. Damage to the mandibular branch of the facial nerve can be avoided by ensuring that the upper end of the incision remains 2·5 cm below the posterior angle of the mandible. Extending the incision posteriorly to the mastoid process improves exposure, avoids the mandibular branch of the VIIth nerve and lessens the risk of retractor damage to the XIIth nerve. Careful identification and handling of both the Xth and XIIth nerves should prevent permanent damage.

The most devastating complication of carotid endarterectomy is a stroke. The total number of neurological deficits in this series was 10 (13 per cent). This incidence is high, and was associated with significant mortality and morbidity. Fortunately, 6 of the 10 patients either fully recovered or were left with a minor disability. This incidence, at first sight, appears to be greater than that usually recorded; however, it includes all postoperative neurological deficits, both transient and permanent, since the difference between them is one of degree. Also included are the strokes that result in death: it is not clear in many reports whether these are included in the calculation of permanent deficits. It can be seen from *Table III*, where the incidence of transient and permanent neurological deficits in this and other series is presented, that our total incidence is similar to that of others. Most reports on carotid endarterectomy are from centres well versed in the technique and they reflect current rather than overall achievements (De Weese et al., 1973; Thompson and Talkington, 1976; Collins et al., 1978). This series is small and includes our total experience with this procedure. We have previously demonstrated a correlation between the experience of the operating team and the success of a vascular reconstruction, namely in femoropopliteal reconstruction (MacGowan, 1969). Thompson has reported a similar correlation in his own large personal series of carotid endarterectomies (Thompson and Talkington, 1976). It is also probable that the results commonly reported in the surgical literature are not a true reflection of the general achievements with carotid endarterectomy. This is borne out by a recent study of 228 consecutive carotid endarterectomies done by the members of the neurosurgical and vascular services of a large institution in a mid-Western state of America (Easton and Sherman, 1976). This independent review revealed a combined mortality and morbidity from postoperative stroke of 21·1 per cent.

It is important to reduce to a minimum the occurrence of neurological deficits after carotid endarterectomy; for the majority of patients a permanent neurological deficit is a disaster which may result in either death or ruinous morbidity. A transient deficit is also a failure, although with less serious consequences for the patient. Of course where the neurological complications induced by surgical therapy are many the overall results of surgery may approach those of long term expectant therapy and the procedure can then no longer be advocated with confidence.

Table II: MORTALITY AND LONG TERM RESULTS OF CAROTID ENDARTERECTOMY

Authors	Operative mortality (%)	Normal or improved long term (%)	Length of follow-up
Present series	7	76	1–7 yr
Fields et al. (1970)	3·6	47	42 mth (mean)
De Weese et al. (1973)	1	88	5 yr
Thompson and Talkington (1976)	2·3	88·9	1–13 yr

Table III: INCIDENCE OF NEUROLOGICAL DEFICITS AFTER CAROTID ENDARTERECTOMY

Authors	Transient deficits (%)	Permanent (%)	Total (%)
De Weese et al. (1973)	15	16	21
Fields et al. (1970)	1·8	7·7	8·5
Collins et al. (1978)	3·0	2·2	5·2
Thompson and Talkington (1976)	0·9	0·7	1·6
Present series (1978)	5·5	8·3	13·8

Postoperative neurological deficits result from cerebral hypoperfusion secondary to clamping of the internal carotid, cerebral embolization or acute thrombosis of the reconstructed vessel. The vigorous debate about the relative importance of either cerebral embolization or hypoperfusion has tended to obscure the role of acute thrombotic occlusion of the reconstructed internal carotid artery in the genesis of postoperative stroke. In this series the commonest proved cause of a neurological deficit was an acute thrombotic occlusion. In 4 of 10 patients with neurological deficits the endarterectomized internal carotid artery was shown to have occluded and in only 2 could occlusion be unequivocally excluded as the cause. Others have recorded similar experiences; Lindberg et al. (1975) reported a 10 per cent incidence of acute thrombotic occlusion in their first 100 operations.

The importance of this observation is that it should be possible to detect acute thrombotic occlusion or technical factors favouring its development by peroperative angiography. Many have disputed the value of routine peroperative angiography at the completion of carotid endarterectomy (Andersen et al., 1978). However, there is no doubt that an impressive harvest has been reported by its proponents. Blaisdell reported a 25 per cent incidence of unsuspected defects detected by peroperative angiography in his earlier experiences with carotid endarterectomy in 1967, and he still advocates routine angiography (Blaisdell et al., 1967; Blaisdell, 1978). More recently, Rosental reported an 8 per cent yield of defects requiring correction detected by peroperative angiography (Rosental et al., 1973). We have recently discovered serious unsuspected defects in 2 patients by peroperative angiography and these were corrected without incident. Clearly an operation which is undertaken to correct an angiographic defect should be shown to have achieved that objective at the time of the operation.

The incidence of early thrombotic occlusion is probably greater than suspected. Certainly the continued absence of symptoms referable to the operated side is no guarantee that the reconstruction is patent, as was demonstrated in 2 of our patients who had follow-up angiography before operation on the other side. Angiography revealed unsuspected occlusion of the recently endarterectomized carotid artery. It is mandatory to confirm the patency of a reconstruction before correcting the contralateral side.

Proper evaluation of carotid endarterectomy in the prophylaxis of stroke requires objective evidence of continuing patency. As, until recently, this could only be obtained by repeated angiography, this evaluation has still to be made. It is to be hoped that recent improvements in non-invasive assessment, especially in carotid imaging with pulsed wave Doppler ultrasound, will finally resolve this issue.

The incidence of either of the other two mechanisms commonly claimed to explain neurological deficits, namely cerebral hypoperfusion and embolization, is difficult to determine. Embolization must be a significant cause of postoperative neurological deficit as spontaneous emboli are responsible for the symptoms that prompt surgery. The incidence of platelet–fibrin emboli during carotid endarterectomy has been reported to be from 15 to 50 per cent; however, the diagnosis is frequenly inferential rather than direct (Akl et al., 1975; Bland et al., 1970). Certainly in our series there was strong inferential evidence that intraoperative cerebral embolization was responsible for 3 of the 10 postoperative neurological deficits. Every precaution must be taken during surgery to reduce the risk of embolization during carotid endarterectomy. Adequate exposure permitting gentle dissection of the carotid vessels is obviously essential. The timing of the procedure may also be of importance. Harrison and Marshall (1977) have reported an apparent periodicity in the thrombotic tendency of carotid lesions: patients operated upon within 4 weeks of a transient ischaemic attack were noted to have a greater incidence of thrombus adherent to the lesion than those in whom surgery was performed after a longer symptom-free interval.

Not only is it desirable to reduce the incidence of cerebral emboli, but it is also important to minimize the neurological consequences of such emboli. Hertzer and his colleagues at the Cleveland Clinic have recently introduced an intriguing twist to the controversy over routine intraoperative shunting during carotid endarterectomy. They suggest that cerebral embolization during dissection of the carotid artery is a significant factor in the aetiology of intraoperative neurological deficits and that carotid shunts may reduce the incidence of permanent stroke by supplying adequate blood to an embolized area to minimize the incidence of permanent neurological deficit (Hertzer et al., 1978).

Transient hypoperfusion of the ipsilateral carotid cerebral territory is yet another potential cause of postoperative stroke which has received considerable attention. Clearly there is a group of patients who are at high risk of inadequate cerebral perfusion during the period of carotid clamping (Callow et al., 1978). Uncertainty exists, however, as to which patients require protection and which method of protection is the best. In common with others we have not found either cross-circulation angiography or carotid stump pressures to be of predictive value (Smith et al., 1976; Gayliss and Mieny, 1977). We have had little experience with the use of local anaesthesia or a combination of it with neurolept analgesia instead of general anaesthesia (Connolly et al., 1977) but have relied upon continuous EEG recordings as a guide to the adequacy of cerebral perfusion. In the past this has not proved in our hands to be especially helpful, but we have recently been impressed with the sensitivity of more modern EEG recorders. We have no experience with such methods of cerebral protection during cross-clamping as hypercarbia, hypocarbia, induced systemic hypertension or hyperbaric oxygenation (Ehrenfeld et al., 1970). Until recently we adopted a policy of selective shunting for 'high risk' patients. This we have now abandoned because of uncertainty as to the accuracy with which such patients were identified. We now use an indwelling arterial shunt routinely during carotid endarterectomy for the following reasons: there are 'high risk' patients who may not be recognized as such; continuous perfusion via a carotid shunt may lessen the consequences of cerebral embolization; and shunting may facilitate a less hurried and meticulous reconstruction. The best results with carotid endarterectomy have been achieved by those who routinely used a shunt. Thompson's results are the bench-mark of carotid surgery (Thompson and Talkington, 1976): his incidence of mortality (0·4 per cent) and of permanent neurological deficit (0·7 per cent) should not only be the aim but the achievement of all who perform carotid endarterectomy for the prevention of stroke.

References

AKL B. L., BLAKELY W. R. and LEWIS C. E. (1975) Carotid endarterectomy: is a shunt necessary? *Am. J. Surg.* **130**, 760–765.

ANDERSEN C. A., COLLINS G. J. and RICH N. M. (1978) Routine operative arteriography during carotid endarterectomy: a reassessment. *Surgery* **83**, 67–73.

BAUER R. B., MEYER J. S. and FIELDS W. S. (1969) Joint study of extracranial arterial occlusion. *JAMA* **203**, 509–518.

BLAISDELL F. W. (1978) Routine operative arteriography following carotid endarterectomy. *Surgery* **83**, 114–115.

BLAISDELL F. W., LIM R. and HALL A. D. (1967) Technical results of carotid endarterectomy. *Am. J. Surg.* **114**, 239–246.

BLAND J. E., CHAPMAN R. D. and WYLIE E. J. (1970) Neurological complications of carotid artery surgery. *Ann. Surg.* **171**, 459–465.

CALLOW A. D., MATSUMOTO G., BAKER D. et al. (1978) Protection of the high risk carotid endarterectomy patient by continuous electroencephalography. *J. Cardiovasc. Surg.* **19**, 55–64.

COLLINS G. J., RICH N. M., ANDERSEN C. A. et al. (1978) Stroke associated with carotid endarterectomy. *Am. J. Surg.* **135**, 221–225.

CONNOLLY J. E., KWAAN J. H. M. and STEMMER E. A. (1977) Improved results with carotid endarterectony. *Ann. Surg.* **186**, 334–342.

DE WEESE J. A., ROB C. G., SATRAN R. et al. (1973) Results of carotid endarterectomies for transient ischaemic attack: 5 years later. *Ann. Surg.* **178**, 258–264.

EASTON J. D. and SHERMAN D. G. (1976) Stroke and mortality rate in carotid endarterectomy in 228 consecutive patients. *Stroke* **8**, 565–568.

EHRENFELD W. K., HOYT W. F. and WYLIE E. J. (1970) Effect of CO_2 and systemic hypertension on downstream cerebral arterial pressures during carotid endarterectomy. *Surgery* **67**, 87–93.

ENGELL H. C. (1973) Studies in cerebral circulation. *Bull. Am. Coll. Surg.* **58**, 7–13.

FIELDS W. S., MASLENIKOV V., MEYER J. S. et al. (1970) Joint study of extracranial arterial occlusion. *JAMA* **211**, 1993–2003.

FISHER C. M. (1951) Occlusion of the carotid arteries. *Arch. Neurol. Psychiatr. (Chicago)* **65**, 346–377.

GAYLISS H. and MIENY C. J. (1977) The incidence of malignancy in carotid body tumours. *Br. J. Surg.* **64**, 885–889.

HARRISON M. J. G. and MARSHALL J. (1977) The finding of thrombus at carotid endarterectomy and its relationship to the timing of surgery. *Br. J. Surg.* **64**, 511–512.

HERTZER N. R., BEVEN E. G., GREENSTREET R. L. et al. (1978) Internal carotid back pressure, intraoperative shunting, ulcerated atheromata and the incidence of stroke during carotid endarterectomy. *Surgery.* **83**, 306–312.

JAVID H., DYE W. S., HUNTER J. A. et al. (1974) Surgical treatment of cerebral ischaemia. *Surg. Clin. North Am.* **54**, 329–355.

LINDBERG B., NORBACK B., SVENDSEN P. et al. (1975) Carotid endarterectomy. *J. Cardiovasc. Surg.* **16**, 161–170.

MACGOWAN W. A. L. (1969) A report of 50 consecutive autogenous vein bypass operations for femoropopliteal obstructions. *Br. J. Surg.* **56**, 575–579.

RADIC A., FINN A., HARAN R. et al. (1977) Incidence of strokes in Dublin. *J. Irish Med. Assoc.* **70**, 591–596.

ROSENTAL J. J., GASPAR M. R. and MOVIUS H. J. (1973) Intraoperative arteriography in carotid thromboendarterectomy. *Arch. Surg.* **106**, 806–808.

SMITH L. L., JACOBSON J. G. and HINSHAW D. B. (1976) Correlation of neurological complications and pressure measurements during carotid endarterectomy. *Surg. Gynecol. Obstet.* **143**, 233–236.

THOMPSON J. E. and TALKINGTON C. M. (1976) Carotid endarterectomy. *Ann. Surg.* **184**, 1–15.

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Synovial actinomycosis of the knee: a case report

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SYNOVIAL actinomycosis of the knee is not reported in the world literature. A case of actinomycosis of the hand due to a human bite is recorded but all other cases are visceral or cervicofacial (Rhangos and Chick, 1964).

Case report

A 32-year-old lady presented with a 4-month history of aching and swelling of the right knee and a past history of trauma with laceration of the skin over the knee. The wound had healed slowly with a small puckered scar. The knee was swollen with a discharging sinus. X-rays showed a huge soft tissue shadow around the knee with no calcification or bony change. Synovectomy was performed removing yellowish-brown hypertrophic tissue with areas of necrosis, calcification and sulphur granules. Histology revealed actinomycotic sulphur granules with Gram-positive mycelia and Gram-negative peripheral rods at right-angles to the main mass. The organism was sensitive to penicillin. The patient was treated with penicillin, 10 mega units, reduced to 4 mega units, daily for 3 months. The knee became pain-free but stiff with no swelling.

Eight years later the patient presented with pain and stiffness of the same knee and a small circumscribed swelling over the popliteal aspect. The X-ray of the knee remained unremarkable.

The popliteal swelling was excised and showed fragments of soft and fibrotic yellow shiny tissue that were infiltrated by acute and chronic inflammatory cells. There were also scattered giant cells throughout the specimen. Colonies of actinomyces were seen surrounded by acute inflammatory cells (*Fig.* 1). *Actinomyces israelii*, an anaerobic organism, was isolated from the tissue.

This organism was identified as follows: one blood agar plate was incubated anaerobically at 37 °C, a Sabouraud plate was incubated at 22 °C and the rest were incubated at 37 °C aerobically. The plates were kept for 10 days and were examined daily.

On the blood plates a few colonies were seen. They were rough, heaped up, small, irregular and opaque. In thioglycollate medium the organism grew as small fluffy balls below the surface of the medium. There was no growth on the aerobic plates. The colonies were Gram-stained which revealed pleomorphic, club-shaped, Gram-positive rods.

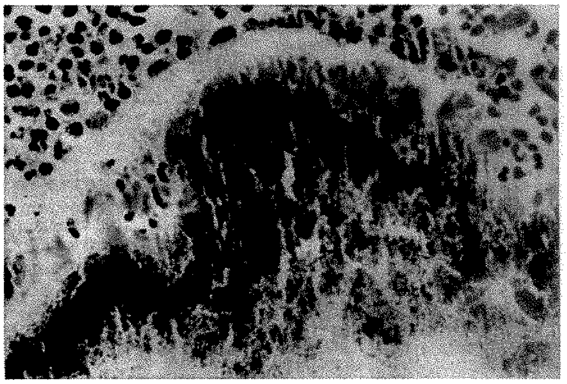

Fig. 1. Photomicrograph (high dry power) of fungi colony with acute inflammatory cells. (×36.)

Further biochemical tests showed that the organisms did not hydrolyse esculin, were catalase-negative, did not produce indole, reduce nitrate or liquefy gelatin.

The patient was treated with penicillin, 10 mega units, reduced to 4 mega units, daily for the next 4 months and remains symptom-free.

Reference

RHANGOS W. C. and CHICK E. W. (1964) Mycotic infections of bone. *South Med. J.* **57**, 664–674.

Paper accepted 8 December 1978.

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The clinical relevance of radiologically revealed Paget's disease of bone (osteitis deformans)

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SUMMARY
Radiological and hospital records of 400 patients with Paget's disease that was shown radiologically have been examined in an effort to establish the clinical significance of the disease. Twenty-eight per cent of the patients were considered to have symptoms related to their disease, the most frequent symptom being bone pain, deformity and fracture. It appears that Paget's disease may predispose to the formation of urinary calculi. Malignant change and neurological and cardiovascular complications are rare, and osteitis deformans does not appear to predispose to osteoarthrosis.

JAMES PAGET first recorded the bone disease that now bears his name in 1877, and of his first patient he said: 'He suffered very little, and engaged in all the pursuits of a country gentleman' (Paget, 1877). His patient presented 20 years previously, with enlargement of the left tibia and femur; 3 years later the skull started to increase in size, and later still the right tibia and femur showed similar changes. The patient died 20 years after presentation following rapid swelling and pain in the left elbow and pleural effusion, indicating malignant change in his bone condition.

Béclère (1901) first recorded the radiological appearances of osteitis deformans, and in 1926 Roberts (a radiologist) and Cohen recognized the subclinical form of the disease. In subsequent papers the proportion of patients considered to be suffering on account of the disease varied from 5 to 80 per cent (Kasabach and Dyke, 1932; Dickson et al., 1945; McKusick, 1966; Evanson, 1974). An opportunity has therefore been taken to make a fresh assessment of the clinical significance of the bone condition in 400 patients with Paget's disease detected radiologically in the course of an epidemiological study of the disease (Barker et al., 1977; Guyer and Clough, 1978).

Patients and methods

Four hundred patients were collected in an unselected manner, as their Paget's disease was detected during a radiological examination, which was not necessarily their first, in local X-ray departments. In most the condition was revealed by plain or contrast examinations of the abdomen, or by skeletal examination, but in some it was detected initially by examinations of the skull, limbs or thoracic skeleton. One hundred patients who had already had extensive radiography now had this extended to provide full skeletal surveys; the extent of their previous skeletal radiology was the only factor considered in their selection. The diagnosis of the disease is based upon standard criteria (Campbell-Golding, 1971), there being three basic radiological forms. The commonest is the spongy form, with coarsening of the trabecular pattern, initially in a normal arrangement but later becoming disorganized. The cortex of the bone becomes thickened and loses its differentiation from the medulla. Areas of lucency are mixed with adjacent areas of sclerosis and eventually bending of the bone occurs due to softening. The second type is the amorphous form ('inactive'), with a dominant sclerosis of the bone which may show increase in diameter; deformity is rare. The third type is the osteoporotic form ('active'), which eventually changes to the spongy or amorphous form, but the process may take many years. Even though the bone is rarefied, it may yet be increased in thickness.

The request cards were examined for mention of Paget's disease, and the reports were studied to see how frequently the visible disease was reported. The case notes of the patients were examined for the clinical reaction to the X-ray report and for evidence that the clinicians attributed symptoms to the bone disease. Possible alternative explanations for pain were sought in the films of the lumbar spine. The notes and the radiographs were also examined for evidence of accepted complications of the bone disease (Campbell-Golding, 1971)—fractures, Paget's arthritis, urinary calculi, vascular calcification, spinal cord compression and sarcomatous change. The pelvis was also examined for evidence of sacroiliac joint fusion (Brunton, 1977). A note was made of both the age at onset of symptoms and the age at which the patient presented with the disease.

Results

Documented evidence of Paget's disease

The examination of the request card revealed that Paget's disease was mentioned in 73 of the 400 patients (18 per cent); in 34 of these the diagnosis had been established radiologically before the initial X-ray in our department. In the remainder, visible clinical deformity (27 patients) or elevation of the plasma alkaline phosphatase (12 patients) generated the request.

The initial radiological report on the anatomical area revealing Paget's disease mentioned the diagnosis in 361 of the 400 patients (90 per cent). The bone disease was generally reported in relation to deformity or fracture, but was, for instance in contrast examinations, often merely a brief comment at the end of the report, if it was mentioned at all.

Cognizance of the X-ray report by the clinician referring the patient for X-ray examination was recorded in the notes or letters of 223 of the 361 patients (62 per cent) in whom the disease was reported. In the 39 patients in whom the disease was not reported radiologically, it was recorded only once by the clinicians.

Table I: COMPLICATIONS OF PAGET'S DISEASE (400 PATIENTS)

Hip joint narrowing	188
Bone deformity	105
Vertebral wedging	39
Pathological fracture	24
Sacroiliac joint fusion	15
Increment fracture	13
Ureteric colic	12
Malignant degeneration	5
Deafness	3
Spinal cord compression	2
Congestive heart failure	1

Complications (Table I)

Bone deformity was present radiologically in 105 patients, being also visible clinically in 33. In 72

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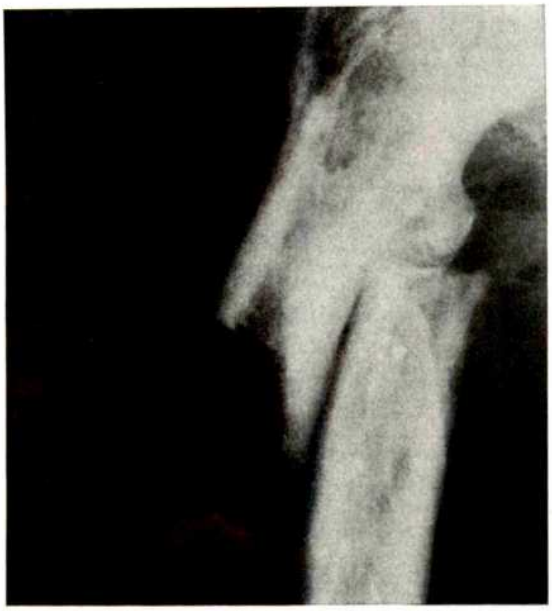

Fig. 1. Typical transverse fracture in the mixed form of Paget's disease. Multiple increment fractures are also visible, represented by transverse radiolucencies on the convexity of the femoral shaft.

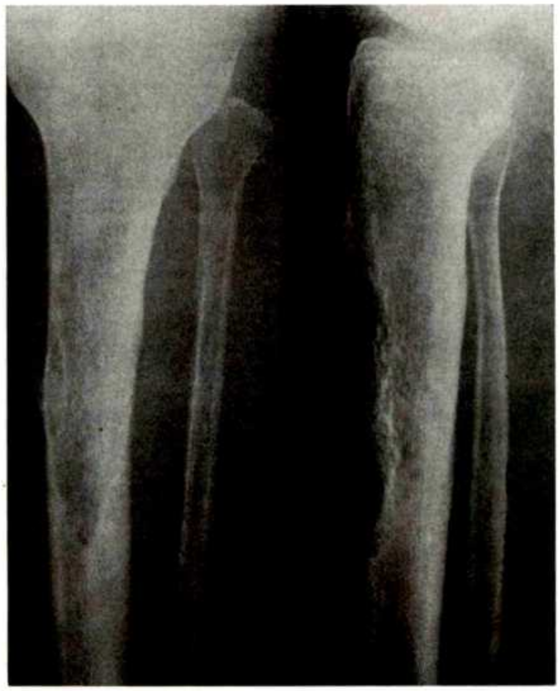

Fig. 2. Paget's disease of the osteoporotic type in the midshaft of the tibia, presenting as a painless swelling. When localized thus, it may be called 'osteoporosis circumscripta'; the sharp lower margin is typical.

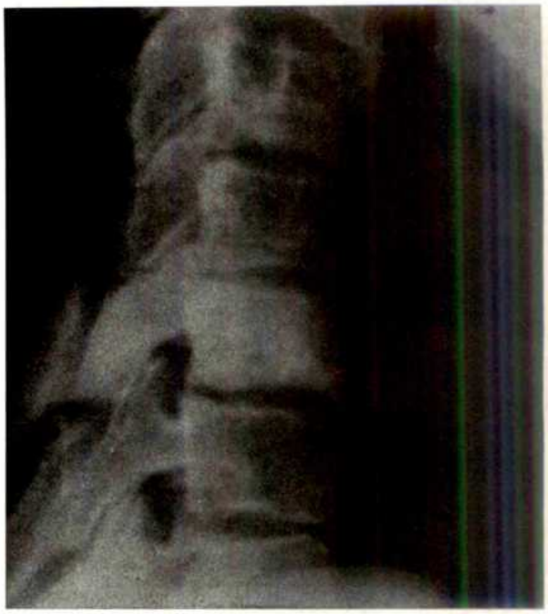

Fig. 3. Sclerosis of C5 vertebra due to the amorphous form of Paget's disease. Involvement of the appendages is characteristic.

patients the deformity was only detected radiologically. Twenty-four of these had basilar invagination, which was found in one-third of those with skull involvement. This is diagnosed when a line drawn from the posterior end of the hard palate to the undersurface of the occiput cuts the odontoid peg more than 6 mm below its apex (McGregor's modification of Chamberlain's line). Forty-eight patients had protusio acetabuli, which was present in varying degrees in 10 per cent of patients with pelvic involvement. Wedging of Pagetoid vertebrae occurred in 39 patients. Evidence of disc degeneration also was visible in films of the lumbar spine in 94 per cent of the 400 patients; 11 per cent had spinal osteoporosis and 2 per cent had secondary deposits. One patient had a fracture of the odontoid peg when the second cervical vertebra was involved by the Paget's disease. In 19 patients, 5 of whom had full skeletal surveys, involvement of a single lumbar vertebra was the only evidence of the disease.

Pathological fracture through Pagetoid bone occurred in 24 patients (*Fig.* 1), being a presenting feature in 22 of these. There were 15 femoral fractures (8 transcervical or transtrochanteric, 2 subtrochanteric and 5 femoral shaft). There were 3 fractures of the humerus, 2 of the tibia and 1 each of the ulna, the odontoid peg, the patella and the pubic rami. Eighteen of the fractures occurred in the mixed form of the disease, 1 in the sclerotic form and the remaining 5 in the osteoporotic form. Only 2 patients had any symptoms before the fracture and 1 of these also had visible Pagetoid deformity. Increment fractures (incomplete fractures, generally on the convexity of long bones) (*Fig.* 1) were present in 13 patients, but none of these patients had any related symptoms.

Sacroiliac joint fusion was visible in 15 patients and partial obliteration of the joints appeared to be present in a further 75 patients. In a few of the latter, oblique

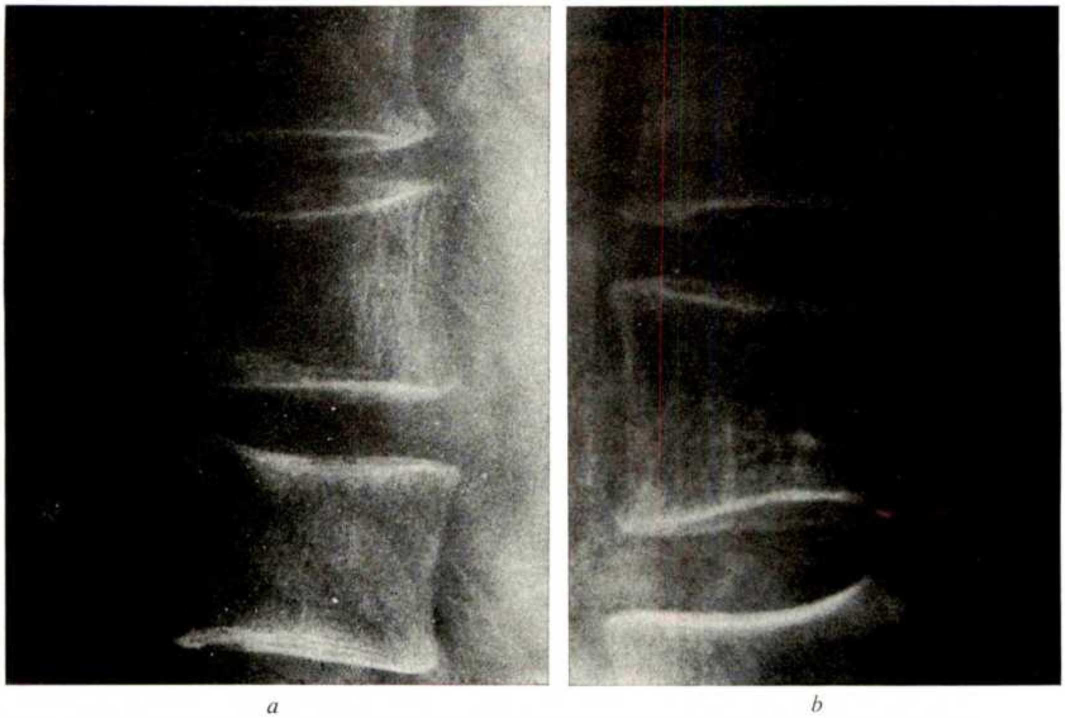

Fig. 4. Osteoporotic Paget's disease of a vertebral body (*a*) with characteristic trabeculation parallel to the vertebral margins, contrasted with the predominantly vertical trabeculation of a haemangioma (*b*).

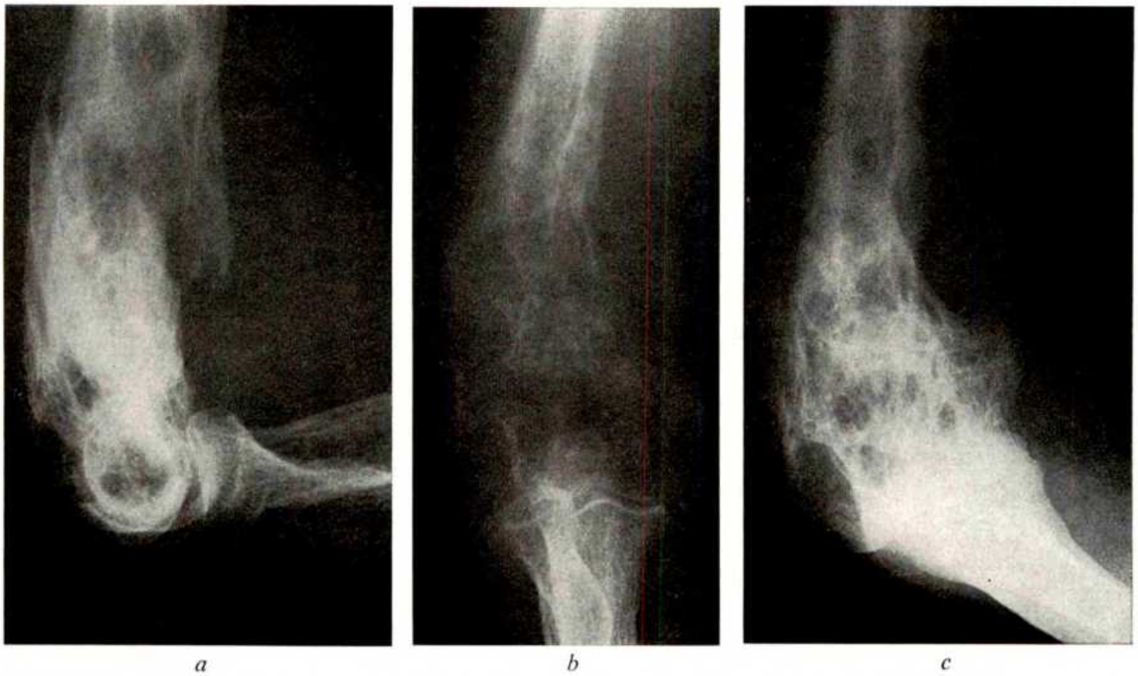

Fig. 5. Fracture in Paget's disease of the mixed form affecting the humerus (*a*), followed by extreme rarefaction associated with immobilization during the acute phase (*b*); this might suggest malignancy were not the initial film available. Final complete healing (*c*).

views indicated that in these the fusion was apparent rather than real.

Three patients had deafness attributed to the Paget's disease. There were no patients with evidence of other cranial nerve involvement. One patient with basilar invagination had evidence of spinal cord compression, and another patient had spinal cord compression due to involvement of the 12th dorsal vertebra.

In 1 patient congestive heart failure was attributed to the bone disease.

Five patients had malignancy complicating their Paget's disease (osteosarcoma in 3, fibrosarcoma in 2); we had no patient with chondrosarcoma or giant cell tumour. In 1 patient with each type of malignancy it was multicentric; in 1 patient the sacrum was involved and in the other 2 patients the femur was affected.

Ureteric colic occurred in 12 patients, and in 5 of these calculi were seen. This frequency of colic is ten times that in the general population (Barker, 1977).

Joint changes were noted in 420 hips of 300 patients with Paget's disease on one or both sides of the hip joint. In 28 hip joints, joint narrowing to less than 3 mm was the only abnormality, and in 330 hips there was evidence of minimal joint degeneration accompanied by a similar degree of joint narrowing. More advanced changes were present in 27 hips.

Frequency of symptoms

In 137 of 361 patients (34 per cent) in whom the disease was reported radiologically, clinicians attributed symptoms to the bone disease (*Table II*). With the exception of the 30 patients who presented with bone pain and the 12 patients who were investigated on account of a raised plasma alkaline phosphatase, all the other patients presented with one of the complications that have already been listed in *Table I*. Painless deformity of bone was the most common presentation (33 patients); 24 presented with pain in joints that were later found to have adjacent Paget's disease, but as will be seen from the discussion below, these symptoms could be coincidental.

Onset and duration of the disease

Thirteen patients were under the age of 55 years at the onset of symptoms; the youngest was a male aged 24 years. Eighteen patients were under the age of 55 at diagnosis. The youngest of these was a male aged 32, and he presented with spinal cord compression due to involvement of the 12th dorsal vertebra. Most patients were aged between 55 and 84, but 11 patients were aged 85 or more. Ten patients have been under observation for between 1 and 20 years with Paget's disease that has so far remained asymptomatic.

Discussion

Clinical suspicion of Paget's disease

The infrequency with which Paget's disease is mentioned on X-ray request cards suggests that clinicians rarely consider Paget's disease as an explanation of symptoms before its radiological detection. In no patient was Paget's disease mentioned on the request card unless the diagnosis had been previously established, or there was clinical deformity, or the patient was being investigated for a raised plasma alkaline phosphatase. Failure to report radiologically visible Paget's disease could be due to a failure of observation or to the consideration that it was irrelevant to the clinical problem.

Table II: CLINICAL SYMPTOMS OR SIGNS AT PRESENTATION IN 137 PATIENTS WITH PAGET'S DISEASE

Bone pain	30
Osteoarthritis	24
Deformity	33
Fracture	22
Malignancy	5
Low back pain	10
Spinal cord compression	1
Raised plasma alkaline phosphatase	12

Symptoms and complications of Paget's disease

Amongst the 105 patients with bone deformity, there were 33 in whom the condition was visible both clinically and radiologically but who were otherwise symptom-free; this is considerably less than the incidence of visible deformity in other series—36 of 116 patients described by Gütman and Kasabach (1936) and 52 of 111 patients recorded by Rosenkrantz et al. (1952). One of the 24 patients with basilar invagination had pressure upon the spinal cord at the foramen magnum.

Of 39 patients with vertebral wedging, only 1 had symptoms attributed to this by clinicians, although 9 others had low back pain. Dickson et al. (1945) state that symptoms are common with this finding, but Barry (1969) considers that it is doubtful whether Paget's disease in the spine ever gives rise to symptoms. He suggests that loss of vertebral height in Paget's disease should be considered a deformity rather than a fracture. The difficulty in ascribing symptoms to Paget's disease of the spine is also indicated by the frequency with which disc degeneration is present, and there was frequently no reason given for attributing pain to Paget's disease rather than to the disc degeneration in this series of patients. Involvement of a single vertebra by sclerotic Paget's disease (*Fig.* 3) may give rise to difficulties in diagnosis, when sclerotic deposits from breast or prostate, bone infection, benign osteoblastoma, lymphoma and osteoid osteoma may all have to be considered and bone biopsy may have to be undertaken (Fairbank, 1951; Brailsford, 1954; Schwartz and Rebeck, 1954; Dennis, 1961; Finby and Begg, 1963). When the osteoporotic form of the disease affects the spine (*Fig.* 4), haemangioma of vertebra is the main differential diagnosis.

Pathological fracture occurred in 22 of the patients at presentation, and as a later complication in a further 2 patients, often following minimal trauma. There were only 2 subtrochanteric fractures of the femur, which Barry (1969) claims to be the commonest site. Five fractures occurred owing to the osteoporotic form of the disease (Grainger and Laws, 1957). This frequency of pathological fracture is only half that of other series (Newman, 1946; Rosenkrantz et al., 1952), probably due to different patient selection in these series. Extreme rarefaction, which may occur in the region of such fractures due to the combination of immobilization and the already pathological bone, occurred in 1 patient (*Fig.* 5), simulating malignancy. In 13 patients there were increment fractures, but none of these patients appeared to have symptoms. Allen and John (1937) suggest that these fractures may become complete, which may have occurred in the patient illustrated in *Fig.* 1. Barry (1969) considers that these result from repeated minor trauma; in no patient in this series with this complication were there recognized episodes of bone injury.

Sacroiliac joint fusion in 15 patients appeared to be complete, and was seen when both sides of the sacroiliac joint were affected by Paget's disease. In no patient was there any history, or pain, to indicate inflammatory sacroileitis, and the cause of this appearance is uncertain; cartilage necrosis similar to that in the hip joint (Campbell-Golding, 1971) may play a part.

Authenticated cases of cranial nerve involvement by Paget's disease do seem to be rare (Kay et al., 1934; Dickson et al., 1945; de Deuxchaines et al., 1964), and the best description of involvement of the orbital nerves was given over 50 years ago (Wyllie, 1923). The relation of deafness to Paget's disease affecting the skull is not clear (Newman, 1946; Clemis et al., 1967; Prestanick, 1969; Nager, 1975). It appears that the mixed sensori-neural deafness could equally well be due to otosclerosis or arteriosclerosis, and current methods of testing do not differentiate. Narrowing of the internal auditory meatuses is rarely demonstrable. The commonest neurological complication is spinal cord compression (Turner, 1940; Latimer et al., 1953; Klenerman, 1966; Cartlidge et al., 1972). Headache is likely to be coincidental (Kay et al., 1934).

Congestive heart failure was common, but in only 1 patient in the series was it attributed to Paget's disease, and even here the extent of skeletal involvement was considerably less than the 30 per cent which is normally considered necessary to cause haemodynamic upsets (Clinicopathological Conference, *British Medical Journal* (1965), pp. 803–6). Well-documented cases of heart failure due to Paget's disease are rare (Alpert, 1958; Harrison; 1958), but a hyperdynamic circulation is common. Both are attributed to increased blood flow through the diseased bone, which may be twenty times normal (Edholm et al., 1945). Other complications, such as valvular and myocardial calcification and peripheral vascular disease, are probably no more common in Paget's disease than in the general population (de Deuxchaines et al., 1964; Guyer and Dewbury, 1978).

There were 5 patients with malignant change and if, as Galbraith (1954) suggests, only 10 per cent of patients in the community who have Paget's disease are seen in hospital, then the frequency of this complication is certainly less than 1 per cent (a figure suggested by Price and Goldie (1962) and Barry (1969)), and is probably in the region of 0·1 per cent. In 28 per cent of patients aged 55 years or more who have bone sarcoma, osteitis deformans is considered to be a predisposing factor (Coley and Sharp, 1931).

Ureteric colic occurred in 12 patients (3 per cent of the series). Slightly greater frequencies of this complication are recorded by Dickson et al. (1945), Newman (1946), Snapper (1949), Rosenkrantz et al. (1952) and Ridlon (1962). Barker et al. (1977) have found an incidence for urinary calculi of 20·7 per 100 000 admissions per annum. The prevalence for this complication amongst the Southampton patients suggests that it is ten times as common in Paget's disease as it is in the general population. Hypercalcaemia and hypercalcuria are known to occur in Paget's disease, particularly at times of inactivity (Goldstein and Abehouse, 1935), but there was no evidence of inactivity in the patients of the present series who had colic.

Graham and Harris (1971), Roper (1971) and Detenbeck et al. (1973) have all expressed difficulty in ascribing joint degeneration and joint symptoms to Paget's disease, the first of these authors stating that symptoms are rare. In a study comparing 300 patients with Paget's disease adjacent to the hip joint (Guyer and Dewbury, 1978) it was concluded that Paget's disease does not predispose to osteoarthrosis but gives rise to specific joint abnormalities, i.e. narrowing of joint space and protusio acetabuli.

Pain associated with Paget's disease

There were 30 patients in whom radiologically detected Paget's disease of bone was used to explain localized bone pain (*Table II*). The pain as described in these patients was of variable severity, of a deep, boring nature and rather constant, being unrelated to joint movement. Less severe pain could be controlled by oral analgesics; more severe pain was regarded as an indication for calcitonin therapy, to which it generally responded if the patient tolerated, and persevered with, the injections. All the patients developing malignancy presented with pain of increasing severity associated with swelling around the malignancy; none of them had had any symptoms before the onset of the pain, which was attributed to the malignant change.

Age of onset of symptoms

The onset of symptoms in 13 patients under the age of 55, and the actual diagnosis of the disease in 18 patients in the same age range, emphasize the fact that Paget's disease is not solely a disease of advancing years. Paget's seventh patient was aged 28, and there are many patients of similar age reported in the literature (Roberts and Cohen, 1926; Kay et al., 1934; Gutman and Kasabach, 1936; Brailsford, 1938; Fairbank, 1951; Seaman, 1951; Collins, 1956; de Deuxchaines et al., 1964). The youngest fully documented patient in the literature is 18 years of age (Wagner, 1947).

Conclusions

If the 24 patients with osteoarthrosis and the 12 with an asymptomatic elevation of the plasma alkaline phosphatase are excluded, there remain 101 out of 361 patients (28 per cent of those in whom a clinical reaction can be judged) who appear to have symptoms attributed to their Paget's disease by their clinicians. This is in keeping with the suggestion, made both by Galbraith (1954) and Collins (1956), that approximately 20 per cent of patients have symptoms attributable to their bone disease, but it must be remembered that in some of those with pain there was no clear reason for attributing this to Paget's disease rather than disc degeneration for example. This is probably offset to an unknown extent by patients who had symptoms due to Paget's disease but which were not recognized as such.

Taking the symptoms and complications together, it is recommended that, apart from those patients who present with complications of their Paget's disease, the condition should continue to be recorded in the notes and reported to the general practitioner when discovered incidentally during radiological examinations, because it may from time to time lead to an explanation of symptoms or to an alteration in diagnosis and management. When initially revealed radiologically, Paget's disease may well be of significance in relation to bone pain, spinal cord compression, ureteric colic, fracture and malignant change; it is not likely to be significant in patients with low back pain, osteoarthrosis, heart failure, headache and cranial nerve palsies. There is evidence that Paget's disease is a progressive process (Guyer and Clough, 1978), so that even though the disease may be asymptomatic on presentation, it may later become symptomatic.

References

ALLEN M. L. and JOHN R. L. (1937) Fissure fractures—their aetiology and clinical significance. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **38**, 109–115.

ALPERT S. (1958) Cardiovascular complications of Paget's disease: a case report. *Ann. Intern. Med.* **48**, 871–876.

BARKER D. J. P. (1977) Personal communication.

BARKER D. J. P., CLOUGH P. W. L., GARDNER M. J. et al. (1977) Paget's disease in fourteen British towns. *Br. Med. J.* **1**, 1181–1183.

BARRY H. C. (1969) *Paget's Disease of Bone.* Edinburgh, Livingstone.

BÉCLÈRE A. (1901) Radiographie d'un cas de maladie de Paget. *Bull. Soc. Méd. Hôp. Paris* **18**, 929.

BRAILSFORD J. F. (1939) Paget's disease of bone. *Br. J. Radiol.* **2**, 507–532.

BRAILSFORD J. F. (1954) Paget's disease of bone. *Br. J. Radiol.* **27**, 435–442.

BRUNTON F. J. (1977) Personal communication.

CAMPBELL-GOLDING F. (1971) In: SHANKS S. C. et al. (ed.) *A Textbook of X-ray Diagnosis by British Authors.* London: Lewis, pp. 737–743.

CARTLIDGE N. E. F., MCCOLLUM J. P. K. and AYYAR R. D. A. (1972) Spinal cord compression in Paget's disease. *J. Neurol. Neurosurg. Psychiatr.* **35**, 825–828.

CLEMIS J. D., BOYLES J. and HARFORD E. R. (1967) Clinical diagnosis of Paget's disease of the temporal bone. *Ann. Otol. Rhinol. Laryngol.* **76**, 611–623.

COLEY B. L. and SHARPE G. S. (1931) Paget's disease—a predisposing factor to osteogenic sarcoma. *Arch. Surg.* **23**, 918–936.

COLLINS D. H. (1956) Paget's disease of bone: incidence and subclinical forms. *Lancet* **2**, 51–57.

DE DEUXCHAINES N. and KRANE S. M. (1964) Paget's disease of bone: clinical and metabolic observations. *Medicine (Balt.)* **43**, 233–266.

DENNIS J. M. (1961) The solitary dense vertebral body. *Radiology* **77**, 618–620.

DETENBECK L. C., SIM F. H. and JOHNSON E. W. (1973) Symptomatic Paget's disease of the hip. *JAMA* **224**, 213–217.

DICKSON D. D., CAMP J. D. and GHORMLEY J. (1945) Osteitis deformans: Paget's disease of the bone. *Radiology* **44**, 449–470.

EDHOLM O. G., HOWARTH S and MCMICHAEL J. (1945) Heart failure and bone blood flow in osteitis deformans. *Clin. Sci.* **5**, 249–260.

EVANSON J. M. (1974) Paget's disease of bone. *Update* February, pp. 331–340.

FAIRBANK H. A. T. (1951) *An Atlas of General Affections of the Skeleton.* Edinburgh; Livingstone.

FINBY N. and BEGG C. F. (1963) The solitary dense vertebral body. *NY J. Med.* **63**, 2995–2998.

GALBRAITH H. J. B. (1954) Familiar Paget's disease of bone. *Br. Med. J.* **2**, 29.

GOLDSTEIN A. E. and ABEHOUSE B. S. (1935) Urinary calculi in Paget's disease. *Am. J. Surg.* **30**, 359–368.

GRAHAM J. and HARRIS W. W. (1971) Paget's disease including the hip joint. *J. Bone Joint Surg.* **53B**, 650–659.

GRAINGER R. G. and LAWS J. W. (1957) Paget's disease—active or quiescent? *Br. J. Radiol.* **30**, 120–124.

GUTMAN A. B. and KASABACH H. H. (1936) Paget's disease (osteitis deformans): analysis of 116 cases. *Am. J. Med. Sci.* **191**, 361–380.

GUYER P. B. and CLOUGH P. W. L. (1978) Paget's disease of bone. *Clin. Radiol.* **29**, 421–426.

GUYER P. B. and DEWBURY K. C. (1978) The hip joint in Paget's disease ('Paget's coxopathy'). *Br. J. Radiol.* **51**, 574–578.

HARRISON T. R. (1958) *Principles of Internal Medicine*, 3rd ed. New York, McGraw-Hill, pp. 691–693.

KASABACH H. H. and DYKE C. G. (1932) Osteoporosis circumscripta of the skull as a form of osteitis deformans. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **28**, 192–203.

KAY H. D., SIMPSON L. S., and RIDDOCK G. (1934) Osteitis deformans. *Arch. Intern. Med.* **53**, 208–248.

KLENERMAN L. (1966) Cauda equina and spinal cord compression in Paget's disease. *J. Bone Joint Surg.* **48B**, 365–369.

LATIMER F. R., WEBSTER J. E. and GURDJIAN E. S. (1953) Osteitis deformans with compression of spinal cord. *J. Neurosurg.* **10**, 583–589.

MCKUSICK V. A. (1966) *Hereditable Disorders of Connective Tissue*, 2nd ed. St Louis, Mosby.

NAGER G. T. (1975) Paget's disease of the temporal bone. *Ann. Otol. Rhinol. Laryngol.* **84**, 1–32.

NEWMAN F. W. (1946) Paget's disease of bone. *J. Bone Joint Surg.* **28**, 798–804.

PAGET J. (1877) On a form of chronic inflammation of bones (osteitis deformans). *Medico. Chir. Trans. (Lond.)* **60**, 37–64.

PRESTANICK J. P. (1969) Tomography of the temporal bone in Paget's disease. *Am. J. Roentgenol. Radium. Ther. Nucl. Med.* **105**, 838–843.

PRICE C. H. G. and GOLDIE W. (1969) Paget's sarcoma of bone. *J. Bone Joint Surg.* **51B**, 205–224.

RIDLON H. C. (1962) Urinary calculi associated with Paget's disease of bone. *J. Urol.* **87**, 499–503.

ROBERTS R. E. and COHEN M. J. (1926) Osteitis deformans. *Proc. R. Soc. Med.* **19**, 13–39.

ROPER B. A. (1971) Paget's disease involving the hip joint—a classification. *Clin. Orthop. Rel. Res.* **80**, 33–38.

ROSENKRANTZ J. A., WOLF J. and KAICHER J. J. (1952) Osteitis deformans (Paget's disease of bone): review of 111 cases. *Arch. Intern. Med.* **90**, 610–633.

SCHWARZ G. A. and REBECK S. (1954) Compression of the spinal cord in osteitis deformans (Paget's disease) of vertebrae. *Radiology* **63**, 48–58.

SEAMAN W. B. (1951) Roentgen appearances of early Paget's disease. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **66**, 581–594.

SNAPPER I. (1949) *Medical Clinics on Bone Disease*, 2nd ed. New York, Interscience.

TURNER J. W. A. (1940) The spinal complications of Paget's disease. *Brain* **63**, 321–349.

WAGNER M. (1947) Report of Paget's disease in an 18-year-old male, with review of literature. *Wisconsin Med. J.* **46**, 1098–1107.

WYLLIE W. G. (1923) The occurrence in osteitis deformans of lesions of the central nervous system with a report of four cases. *Brain* **46**, 336–351.

Paper accepted 24 October 1978.

Correspondence

On survival rates in surgical treatment for ischaemic leg

Sir,

I find it difficult to see how Dr Boba's interpretation of our findings (*Br. J. Surg.* 66, 293) differs from our own. We also consider that our results give no cause for optimism. Few vascular surgeons consider the long term fate of their patients with anything but pessimism. We have presented the data in an attempt to help each surgeon assess 'whether the early risks of surgery and the late risks of death from general causes . . . warrant salvage surgery'.

I suspect that most surgeons will be unable to follow Dr Boba's concept that a force '. . . tends to displace the individual from a condition of being alive to one of being dead . . . .' In practice, we find that death is a precise event. However, if a colloquial analogy is that we are all dying slowly and the vascular patient is dying rather more quickly, then the concept is hardly remarkable.

I do not understand why Dr Boba presents 'alternative conclusions', for they are identical to our own, though worded very differently. Certainly, the presence of clinical atherosclerosis and its treatment worsen survival rates. The operations discussed are designed to save the leg, not the patient. Certainly, amputation is the easy way out, and may well involve the least physical trauma though at the expense of psychological distress and a considerable burden on relatives and the community. In the discussion, we stressed that the results should not influence the choice of operation.

Dr Boba presumably does not understand that a successful salvage operation allows far quicker ambulation than does amputation. Finally, it goes without saying that vascular surgeons advise appropriate changes in lifestyle as part of general management.

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Anterior highly selective vagotomy

Sir,

We have read with great interest the article by Messrs Hill and Barker entitled: 'Anterior highly selective vagotomy with posterior truncal vagotomy: a simple technique for denervation of the parietal cell mass' (*Br. J. Surg.* 65, 702–705). For some time we have been performing anterior highly selective vagotomy with posterior truncal or selective vagotomy in an attempt to preserve an adequate blood supply to the lesser curve of the stomach. Anterior highly selective vagotomy with posterior selective or truncal vagotomy has been performed in 4 patients with uncomplicated duodenal ulcer. The diagnosis was confirmed at the operation. There were 3 males and 1 female of mean age 31 years. In 2 cases we have performed anterior highly selective vagotomy with posterior selective vagotomy and in 2 cases, anterior highly selective vagotomy with posterior truncal vagotomy.

Two weeks after the operation the mean percentage reduction of basal acid secretion was 71 per cent and maximal, after histamine, was 55 per cent. Hollander's test was negative. The reduction of acid secretion achieved after this type of vagotomy is very similar to results after highly selective vagotomy in our patients (mean reduction of BAO, 75 per cent; MAO, 50 per cent).

Of our 103 cases of highly selective vagotomy, ischaemic necrosis of mucus membrane of the lesser curve occurred in 2. Necrosis was confirmed by gastrofibreoptic examination and subsided after medical treatment. Therefore, we carried out an investigation on the blood supply to the lesser curve of the stomach after highly selective vagotomy. In conclusion, we think that the only way of preventing ischaemic necrosis of the lesser curve after highly selective vagotomy is by performing anterior highly selective vagotomy and posterior truncal or selective vagotomy. The vessels of the posterior leaf of the gastrohepatic ligament ensure blood supply to the lesser curve of the stomach.

In our patients operated in this way the gastrofibreoptic picture of the mucus membrane of the lesser curve in the early stage (3 days) after the operation was normal. Gastric secretion (basal and maximal) decreased in a similar manner to that seen by Hill and Barker. The Hollander test was negative. Gastric emptying as assessed by radiological examination in the early stage after operation was not delayed.

If the late results of this kind of vagotomy are as good as those after highly selective vagotomy, it seems that this modification may prevent necrosis of the lesser curve of the stomach.

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Book reviews

An Introduction to the Symptoms and Signs of Surgical Disease

Norman Browse. 245 × 185 mm. Pp. 409+viii. Illustrated. 1978. Edward Arnold: London. £12·75.

THE author's declared intention in producing this book has been to emphasize to our medical undergraduates the need to acquire proper techniques in clinical skills such as history-taking and clinical examination. There is no doubt in my mind that he has achieved this main objective, as the book consists of a simple, clear and well-structured account of this rather loosely defined subject. In addition, the text contains a considerable amount of essential core knowledge relevant to clinical practice, together with revision panels which should be of considerable help to the student and the newly qualified houseman.

Occasionally, I did find the text to be too dogmatic when it need not have been so, and I am sure that not everybody would agree with all its statements. Nevertheless, this is inevitable, as clinical practice must always relate in the end to the individual practitioner. It does, however, reflect in the main the general consensus of opinion and the book should be strongly recommended to undergraduates. Perhaps the book would gain by the inclusion of some colour illustrations, but no doubt this would add further to the cost, which at the present level of £12·75 is probably already on the expensive side for the average student.

A. CUSCHIERI

Reanimation of the Paralyzed Face. New Approaches

Edited Leonard R. Rubin. 280 × 210 mm. Pp. 367. Illustrated. 1977. St Louis: Mosby. No price given.

TEN years ago the treatment of the paralysed face was relatively simple but there has been a plethora of new techniques, including microsurgery, which has altered the picture. This book describes many of the techniques simply and well. It discusses their relative merits and disadvantages without bias. They all have some drawbacks and further developments and refinements are expected.

The presentation is good. Each chapter is succinct and starts with a short summary. The book is well illustrated, both by line drawings and by monochrome photographs; there is a very useful bibliography. There are nine contributors, most are from North America, but included are the pioneers of microneural repair from Europe, Millesi and Anderl. The microvascular work is covered by Harii and Ohmori from Japan. As well as plastic surgeons, neurologists, ENT surgeons, a pathologist and a specialist in rehabilitation have written chapters.

The book is divided into four parts. Part One covers the anatomy and the physiology of nerve and muscle damage; Part Two the causes of facial paralysis; Part Three the techniques of free nerve and muscle grafting, and the largest section, Part Four, the actual management of cases, both immediate and after months and years.

The book should be read by all who have an interest in this field and my only reservation is that some of the older techniques are abandoned. For instance, the static sling, it is said, 'should not be used under any circumstances'. Hypoglossal facial anastomosis is only briefly mentioned. Tarsorrhaphy is not discussed, nor does the editor approve of weights, magnets or slings around the eye. There is no mention of the help that rhytidectomy can give to the late case. Yet this is a book on 'new approaches' and this topic is covered well.

B. MORGAN

A Course in Renal Disease

Geoffrey M. Berlyne. Fifth edition. 215 × 140 mm. Pp. 450+x. Illustrated. 1978. Oxford: Blackwell Scientific. £6·75.

THE fact that this book is now in its fifth edition in 1978 having been first published in 1966 speaks for its popularity. The book is designed to sustain the reader's interest by posing questions at frequent intervals. The scope of the text is wide and once the basic anatomy and physiology have been covered then more detailed nephrological topics are discussed. There is no doubt that this volume has greater value for the physician than the surgeon, but nevertheless the sections dealing with physiology, hypertension, acute renal failure, therapeutics and specific surgical diseases of the kidney will be of undoubted interest and value to the surgeon.

This volume cannot be described as essential for the private surgical bookshelf, although its presence in the library would be beneficial as certain topics are presented clearly and in a fashion that holds the reader's attention.

F. THOMPSON

A Simple Guide to Trauma

R. L. Huckstep. Second edition. 190 × 120 mm. Pp. 250. Illustrated. 1978. Churchill Livingstone: Edinburgh. £2·95.

SIMPLE is the word for this excellent little book. As an aide-mémoire for students of medicine, nursing and allied disciplines, it is almost unbeatable and there can be few more experienced practitioners who will not find something of value within it. If I have any criticism, it is of the format. The ring binding is deplorable and I feel that Professor Huckstep has in this respect, and this respect only, been rather let down by his publishers, but doubtless they will remedy the matter when the third edition comes along, as indeed it must.

J. G. P. WILLIAMS

Malignant Diseases of Infancy, Childhood and Adolescence

Arnold Altman and Allen D. Schwartz. 255 × 175 mm. Pp. 531+x. Illustrated. 1978. Eastbourne: Holt–Saunders. £20·00.

THE eighteenth volume in the series *Major Problems in Clinical Paediatrics* is devoted to malignant diseases of infancy, childhood and adolescence. Edited by two paediatric haematologist–oncologists, it is directed primarily at the practising general paediatrician who is confronted only rarely with this potentially lethal condition. The major emphasis is on the diagnosis of malignancy and on the recognition and treatment of life-threatening complications. The natural history and prognosis of the various conditions are delineated. The treatment of malignant disease is becoming increasingly complex and demands the establishment of specialized regional centres with multidisciplinary cooperation. The authors wisely omitted details of many treatment protocols that have not become firmly established and limit their discussion to those regimens which are fairly standardized and successful. The sections on oncologic emergencies and on the psychological and social support of the patient and family are particularly relevant to the primary physicians and equally instructive for the multidisciplinary team engaged in the acute management and long term care. The text is well written and concise and the references are comprehensive and up to date. The book is modestly priced by present standards. I would strongly recommend it for all those individual specialists engaged in the management of children with malignant disease despite the fact that surgical management is only briefly discussed.

LEWIS SPITZ

Scoliosis and Other Spinal Deformities

John H. Moe, Robert B. Winter, David S. Bradford and John E. Lonstein. 270×190 mm. Pp. 691+xix. Illustrated. 1978. Eastbourne: Holt–Saunders. £21·00.

THIS book is an outstanding contribution to the practice of spinal surgery. The four authors constitute the staff of the famous Twin Cities Scoliosis Centre at Minneapolis which has done much to pave the way in the surgical management of spinal deformities. This publication documents their views after 25 years' experience.

The introductory part includes detailed and useful chapters on patient evaluation, the normal development of the spine, and the natural history of untreated spinal deformities during childhood and adult life. The different types of scoliosis from the common idiopathic curve to that seen in association with Marfan's syndrome are then considered. There is a valuable contribution on the spinal deformities in myelomeningocele which reflects the relatively large numbers of adolescent spina bifida patients being seen at present. After sections on Scheuermann's kyphosis and adult scoliosis there is a series of shorter chapters on spinal infection, trauma and the deformities seen in the different types of dwarfism.

The emphasis throughout the book is on the practical management of these conditions, and in particular space is given to the details of surgical methods and possible complications. Techniques in plaster casting and brace orthotics are described thoroughly.

Just as Professor J. I. P. James's book on scoliosis has become the standard reference of the resident training in spinal surgery, this volume must have a similar role for the consultant specializing in the treatment of spinal deformities. One minor criticism which arises when one compares these two works concerns the Minneapolis book's dismissal of the aetiology of idiopathic scoliosis in one paragraph.

This publication is a 'must' for the book shelves of orthopaedic, thoracic and neuro- surgeons concerned with spinal deformities, where, before long, it will undoubtedly become a well-thumbed classic.

M. EDGAR

General Urology

D. R. Smith. Ninth edition. 260×180 mm. Pp. 541+ix. Illustrated. 1978. Los Altos: Lange. $14.50.

THIS is a new edition of a well-established textbook intended for medical students and junior hospital doctors. There is plenty of information in the book, but little discussion on the surgical aspects of treatment; for instance, the techniques of prostatectomy occupy less than half a column, and retropubic prostatectomy is discussed in three lines. Postoperative management is omitted.

There are good sections on the newer types of investigations, such as renography, renal scanning, ultrasound and CT scanning, but modern urodynamic techniques are dismissed as being too esoteric. The quality of X-ray reproduction is not satisfactory, including one X-ray being upside down. This book is competing against other good urological textbooks and I rather fear that its pages will remain unturned in the average medical school library.

P. H. L. WORTH

Critical Resection Length and Gap Distance in Peripheral Nerves

G. Orf. 230×155 mm. Pp. 91+viii, with 45 illustrations. 1978. Berlin: Springer-Verlag. No price given.

THIS monograph describes the results of stretching the sciatic nerves of 56 giant rabbits and reviews the relevant literature. From the results the critical resection length for these nerves was determined. This is the length which limits direct end-to-end suture. It appears that the length is about 3 per cent.

The book will be of interest to surgeons concentrating on the peripheral nervous system, and to thesis writers, for whom it is exemplary.

M. WATSON

Vascular Trauma

Norman M. Rich and Frank C. Spencer. 265×190 mm. Pp. 610+xiv. Illustrated. 1978. Eastbourne: Holt–Saunders. £27·00.

NOWHERE more than in military surgery is it true that progress is by rediscovery. History tells the same story at intervals down the years. From Ambroise Paré to the large company of vascular surgeons who served in Viet Nam this great, definitive book at last sets these lessons in clear and rational order. Colonel Rich and Dr Spencer, both distinguished in their specialty, have at one time set out the landmarks, stated the aphorisms and shown the way ahead. They give tribute to the 600 young American surgeons whose careful work and clear records during the stressful years 1965–72 provided the data in thousands of arterial repair operations, with a striking and even success rate that more than anything proved the soundness of the principles learned in the earlier conflict in Korea.

In this book there is no padding. All the space is filled with useful facts, demonstrations and advice. From the vast mass of information in this memorable text a reviewer can only draw what he feels to be a few good examples of this helpful style of authorship: such as the incidence of anatomical anomaly of the popliteal, the widely differing operative tactics for coeliac and superior mesenteric injuries, nerve involvement in a false aneurysm and the fine colour plate of a contused, intact but occluded brachial. The text itself is clear and easy to read. It is fine testimony to much magnificent effort.

H. H. G. EASTCOTT

1978 Year Book of Surgery

Edited Seymour I. Schwartz et al. 200×135 mm. Pp. 550. Illustrated. 1978. New York: Year Book (London: Lloyd–Luke). £18·50.

MOST readers will be familiar with this series and the 1978 edition lives up to the high standard of previous volumes. The layout and print are excellent with illustrations, X-rays and charts clearly reproduced so that the book is a pleasure to read. There is an opening chapter reviewing most of the recent advances in surgery of the year and the rest of the book is well arranged in chapters according to anatomical site, with a large section on the different aspects of cardiac surgery.

Like all publications of abstracts of papers it is somewhat indigestible with so much information in a relatively short book. However, one of the most valuable features of the book is the comment by the editor at the end of each chapter. These are nearly always helpful, often critical and sometimes acid, but they do add to the balance of the book and the reader finds himself full of admiration for the knowledge and erudition shown by the editors in presenting and criticizing these papers.

H. E. LOCKHART-MUMMERY

Pheochromocytoma

W. M. Manger and R. W. Gifford jun. 265×190 mm. Pp. 398+xxiv, with 132 illustrations. 1977. Berlin: Springer-Verlag. DM113.10; US $49.80.

PHAEOCHROMOCYTOMA is a rare tumour, but is well described in the literature. However, this is probably the first monograph to be devoted to this subject exclusively, and the authors, both physicians with special experience of hypertension, are to be congratulated on a superb work. They describe and discuss all aspects in a systematic, thorough and clear manner, providing a comprehensive list of over 1000 references, and they draw on their own experience, particularly of the use of measurements of catecholamines in the plasma for the diagnosis and localization of tumours.

The sections on anaesthesia and operative removal of phaeochromocytomas are inevitably derived from the experience of others and they would have been more authoritative and helpful if they had been written by an anaesthetist and a surgeon.

Nevertheless this is a very valuable reference book which all medical libraries should possess and which individuals with a special interest in the subject will wish to buy.

R. B. WELBOURN

Operative Surgery

General Editors C. Rob and R. Smith.

Neonatal Surgery

P. P. Rickham, James Lister and Irene M. Irving. Second edition. 245×180 mm. Pp. 621+xii. Illustrated. 1978. London: Butterworths. £42·50.

THE first edition of this excellent book was published in 1969 as by P. P. Rickham and J. H. Johnston. The latter author has not been excluded! As might be expected, he contributes an admirable urological section. The three authors now named are in fact the main contributors of a total of twenty from Liverpool and Zurich. The book is encyclopaedic in the best sense of the word. The first eight chapters are on general subjects, including the ethics of neonatal surgery and the organization of a regional neonatal surgical service, as well as the customary clinical aspects, which are thoroughly covered. The remainder of the book deals with paediatric surgery in a systematic fashion including the cardiovascular system. Historical, embryological and aetiological aspects are covered before the clinical picture, investigation and management. Operations are mostly described in less detail. Each chapter gives the results obtained in the clinics in Liverpool or Zurich. The style of writing is commendably clear, and surprisingly uniform for a multi-author book, and is well up to date. In management, precise instructions are given. The references are full (but surely it is time the old howler of Wyllie G. G. and Adelaide M. B. as co-authors in the *Lancet* 1957 article referred to on p. 455 was laid to rest).

It is inevitable that in detailed contributions such as these there will be some areas of disagreement. The section on Hirschsprung's disease comments on Ehrenpreis's hypothesis that the muscle of the aganglionic section is the seat of denervation hypersensitivity (p. 422), whereas the work of Garrett and Howard and others suggests that the abnormal extensions of the preganglionic fibres into the muscle layers make effective contacts. Nor would I consider the risk of formal rectal biopsy any less than that of suction biopsy which can be applied with so much less disturbance of a possibly sick newborn, although I agree that neither technique is entirely free of risk in practice. Also it is presumably an oversight that the stress of asphyxial birth is not included in the list of risk factors which should lead to particularly careful observation for early signs of necrotizing enterocolitis. But these are relatively trivial matters in a book which must become the standard reference text on the subject for years to come.

H. H. NIXON

Loss and Grief in Medicine

Peter Speck. 198×128 mm. Pp. 175+xiii, with 3 illustrations. 1978. London: Baillière Tindall. £2·95.

THIS book is a very timely publication. It comprehensively discusses the management of death and grief in medicine and is easy and interesting to read. Loss and grief are subjects that rarely find a place in surgical journals. This is reflected in the bibliography of the book which contains a noticeably small proportion of references to medical and surgical as opposed to nursing and behavioural journals and monographs. The book describes the surgical situations in which loss followed by grief may occur—amputation, mastectomy, colostomy etc. It describes how grief may be anticipated and understood, how long grief lasts and the role of doctors and nurses in its management.

For me the last section of the book, which dealt with different religious and ethnic reactions to grief, was most illuminating. We now live and work in a multi-racial society and it is imperative that surgeons know the cultural impact that operations may have and what rituals must be attended to when a patient, who is not a member of one of the long-established indigenous religions, dies. The author must be congratulated on producing a compact and informative book which can confidently be recommended to all who practise the art and craft of surgery.

H. BRENDAN DEVLIN

Metabolic Surgery

Henry Buchwald and Richard L. Varco. 235×155 mm. Pp. 317, with 57 illustrations. 1978. New York: Grune & Stratton. No price given.

THIS book is composed of a series of review chapters dealing with a variety of topics related to surgery, each by an author eminently qualified to discuss his own particular field. The overall title of the book, *Metabolic Surgery*, is perhaps a little misleading as the book includes chapters that would seem to describe types of surgery with relatively few metabolic implications. For example, there is a chapter about the spleen which describes features of the haematological and oncological significance of that organ rather than any particular metabolic aspect. However, the authors may feel that the inevitable metabolic changes associated with any form of surgery should imply that almost any surgical topic might be included under this particular title.

It is useful to see reviews in the same book on theoretical and practical aspects, together with the results of management of difficult surgical problems such as obesity by means of gastric and ileal bypass. There is also a comprehensive discussion of the place of intestinal bypass and portacaval shunting in the management of the hyperlipidaemias and glycogen storage diseases.

A number of the chapters hold a particular interest because their topics are unfamiliar in most surgical texts, the chapters on the role of pulsing electromagnetic fields and functional neurosurgery being noteworthy.

In conclusion, although the title of this book is a little misleading, the contents include a number of excellent reviews of current surgical topics which are worth further study.

P. D. WRIGHT

Carcinoma of the Oesophagus: Proceedings of the First South African Conference on Carcinoma of the Oesophagus, Cape Town

Edited W. Silber. 235×155 mm. Pp. 474+xi. Illustrated. 1978. Rotterdam: Balkema. £21·00.

THIS book records the proceedings of the First South African Conference on Carcinoma of the Oesophagus, held in Cape Town in January 1977. As would be expected in view of the site of the conference and the very high incidence of oesophageal cancer in the native population of South Africa, especially in the Transkei, the majority of the speakers came from South Africa, but the programme also included papers from known experts in this subject from Europe, Japan and North America. The early sessions of the conference were devoted to the epidemiology of the condition, with excellent accounts of the widely varying incidence of this condition in different parts of the world and of its apparent increase in the Transkei in recent years, together with discussion of the possible aetiological factors. The major portion of the conference was concerned with the clinical and pathological features of the disease, its diagnosis and the difficult problems of its treatment, problems often exacerbated in Black patients in South Africa by severe malnutrition and concomitant pulmonary tuberculosis. Various papers report the results of radiotherapy and surgical excision in several large series of patients, and there are interesting accounts of treatment plans involving both these modalities, sometimes combined with chemotherapy, together with the use of the various types of intubation, either during the course of attempted curative treatment or as the principal method of restoring swallowing in those patients in whom cure is impossible.

This book covers all aspects of the problems presented by this terrible disease and it is undoubtedly a mine of information. Its value is enhanced by the extensive references included at the end of most of the contributions. The book suffers, however, from the fact that it is apparently a verbatim record of the conference, and its value would have been greatly increased by careful pruning and editing. This is not a book for the general surgical reader, but rather for the specialist with a particular interest in this condition, who will certainly find in its pages much to interest him.

L. P. LE QUESNE

Clinical Anatomy of the Heart

Robert Walmsley and Hamish Watson. 245 × 191 mm. Pp. 229. Illustrated. 1978. Edinburgh: Churchill Livingstone. £22·50.

In this book the authors set out to bring the traditional anatomical descriptions of the isolated heart into a more realistic clinical and radiological perspective. It follows the familiar lines of an anatomical text backed up by numerous radiographs and vertical and transverse whole body sections. No allowance is made for alterations in the anatomical relationships with age, posture, stature, obesity, respiration and cardiac hypertrophy.

In the first chapter there is an abbreviated description of the embryology of the heart, which would be insufficient for the primary fellowships: it omits a description of separation of the truncus and explanation of the common congenital abnormalities met in surgery—Fallot's tetralogy, transposition of the great arteries etc.

Some of the illustrations are not very clear and others might be interpreted differently—the X-ray *Fig.* 1.39 on p. 47 looks more like a pneumonectomy than a lobectomy. Most surgeons would agree that the oesophagus may be indented by the left main bronchus as shown in *Figs.* 4.1, 4.2 and 6.12, yet *Fig.* 4.13 attributes the indentation to the right main bronchus. There is little place for schematic drawings in an anatomical text (*Fig.* 9.11). Other illustrations show a degree of artistic licence which could be misleading, e.g. the left coronary artery in *Fig.* 4.5. The text uses a number of archaic anatomical terms, e.g. 'margo acutus' and 'brachiocephalic artery', and generally lacks clinical familiarity; for instance, why call it the 'anterior descending (interventricular) artery' when most of us know it as the left anterior descending or just LAD.

The description of the fibrous skeleton of the heart is useful, but needs to be tied up with surgical experience at valve replacement and in the preparation of homograft valves. The descriptions of the coronary arteries and conductive tissue are insufficient for the clinical needs of surgeons, e.g. how to avoid putting a stitch in the bundle while closing a VSD or replacing an aortic valve or in the coronary sinus while replacing a mitral.

As John Kirklin says in the foreword, this book has provided some important clinical material. To my mind it will be of use to anatomists and pathologists for occasional reference, but I cannot see it being kept readily at hand in the wards, or in the operating theatre, and least of all on the clinician's own desk or bedside table and, after all, 'clinical' means 'at the bedside'.

J. W. JACKSON

Surgical Pediatric Urology

Edited H. B. Eckstein, R. Hohenfellner and D. I. Williams. 295 × 225 mm. Pp. 533+ix, with 1120 illustrations. 1977. Eastbourne: Holt–Saunders. £66·25.

The three editors of this book have for the first time attempted a comprehensive review of the operations currently in use for all the commonly encountered urological disorders of childhood. To assist them in this task they have assembled a team of distinguished contributors from Europe and America, each writing upon a subject of which he or she has made a particular study. The result is a magnificent volume, a work of major importance in the field of paediatric urology.

The book is aimed at those who have already acquired the basic surgical skills and who either intended to pursue a career in paediatric urology or who wish to develop a deeper interest in the subject, although the editors are careful to stress that some of the procedures described should only be attempted by those who have access to the full back-up services provided by a modern paediatric specialist centre.

Throughout, the emphasis is on operative technique, the intention being that the work should be complementary to the standard paediatric urological textbooks which will provide more complete clinical and diagnostic detail. Despite this, there is an excellent first section which reviews the available diagnostic techniques and discusses overall surgical management. This includes chapters on nursing care, anaesthesia and oncology as well as outstanding contributions on paediatric nephrology and imaging.

As befits a textbook of operative surgery, illustrations are used extensively to clarify the steps of the individual operations. Here the editors have been fortunate in their choice of Rudolf Brammer, who has illustrated the book throughout and has produced more than a thousand drawings of outstanding quality. These are used to particular effect in the chapters dealing with ureteric reimplantation, pyeloplasty and hypospadias repair where a number of alternative techniques have to be described, although the orientation of some of the drawings of intra-abdominal procedures is at times confusing.

The approach to some problems and the spelling and use of some words (as, for instance, in the chapter on testicular tumours) may make English readers a little uncomfortable, but such vagaries are hardly surprising in a work which is aimed at an international readership. Generally all interests are well catered for and there are detailed chapters on haemodialysis and transplantation as well as an unusually long section on urinary tract trauma. Most of the authors have followed their operative descriptions by brief comments on postoperative care and the management of possible complications, whilst at the end of the volume there is an elegant chapter which discusses the long term results of the various procedures.

The choice of print and the layout of the text make the book easy to read, whilst the binding is properly substantial and should withstand repeated handling.

This beautifully produced volume achieves all its aims. The price is high, but nevertheless it represents excellent value for money.

R. MORGAN

MGH Textbook of Emergency Medicine

Edited Earle W. Wilkins. 260 × 180 mm. Pp. 829+xviii. Illustrated. 1978. Baltimore: Williams & Wilkins. No price given.

This massive book is the joint work of sixty-two contributors, all of whom are part of the Emergency Medical Services of the Massachusetts General Hospital. The organizational skills required to achieve this synthesis are of themselves to be admired and much of the content is admirable. The production is superb and the line drawings, like so many in texts from the United States, are in the direct line of Max Brödel with a clarity and directness that it is impossible to fault. As a reference source it will be difficult to improve upon. And yet if one really wants to know what to do, and when, the text is often less than helpful. To be told 'that fiberoptic esophagogastroscopy and selective endoscopy are major recent contributions to the management of profuse gastrointestinal bleeding', but not to be told when to use these investigations and in what degrees of bleeding is frustrating. Many of the statements encountered are empty, for example: 'the mounting availability of selective angiography not only for diagnosis but also for therapy has given the physician a new option and . . . has caused a shift of emphasis away from immediate surgical treatment'. But what options; how has the emphasis shifted; how does it influence the way the next case should be handled? These things we are not told. Similarly in the relatively short section on abdominal trauma, peritoneal lavage (as distinct from tap) is not mentioned; truisms appear such as 'a patient with a traumatic abdominal injury [*sic*] should be closely attended at all times and if his condition deteriorates he should be treated promptly—by laparotomy if necessary'; and we are told that 'radionuclide scanning and arteriographic examination may be useful in patients in whom the diagnosis is suspect', but we are given no idea when these investigations are used.

A skilled craftsman is rightly a little suspicious of multipurpose tools: they usually do all the tasks a little less well than specialized single-use instruments. I have the same feeling about this book. Having edited a similar, though more limited volume in the emergency field myself, I know the difficulties of marshalling disparate facts and opinions. However, in this area, as in no other, direct practical advice is vital, but unfortunately there is little of it here.

H. A. F. DUDLEY

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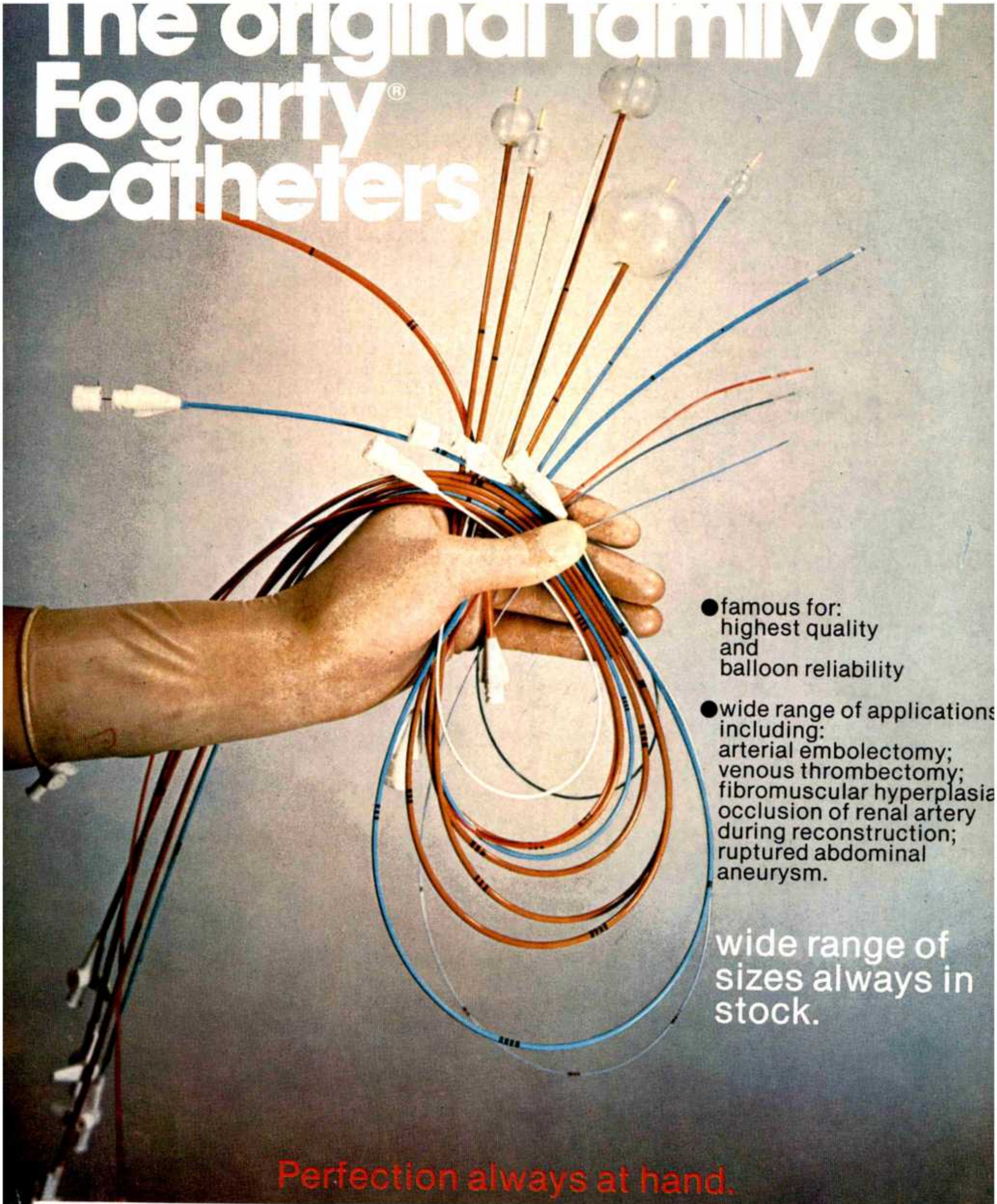

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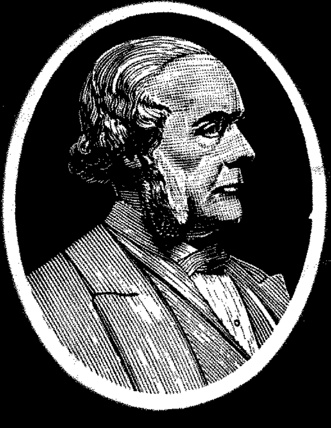

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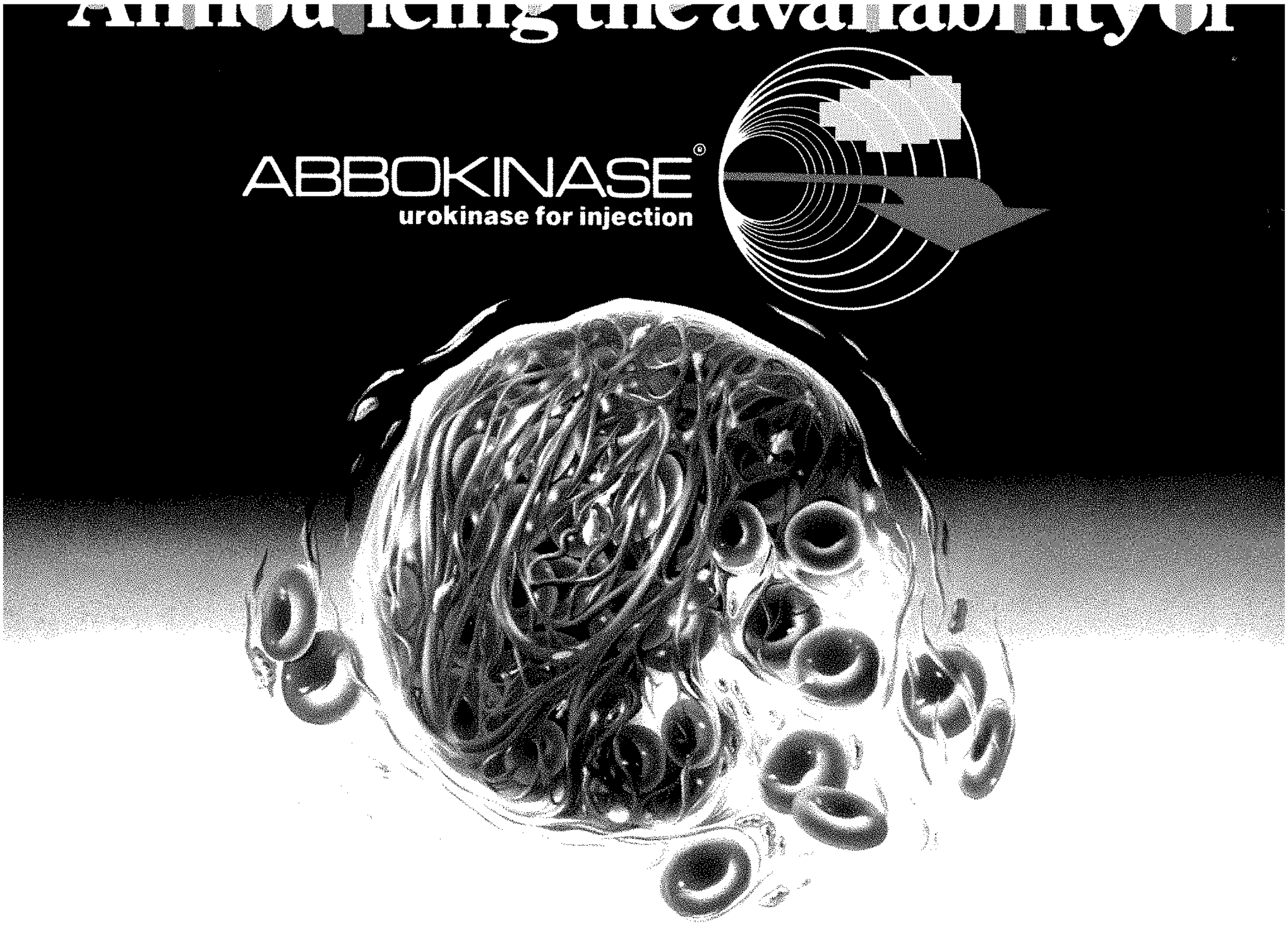

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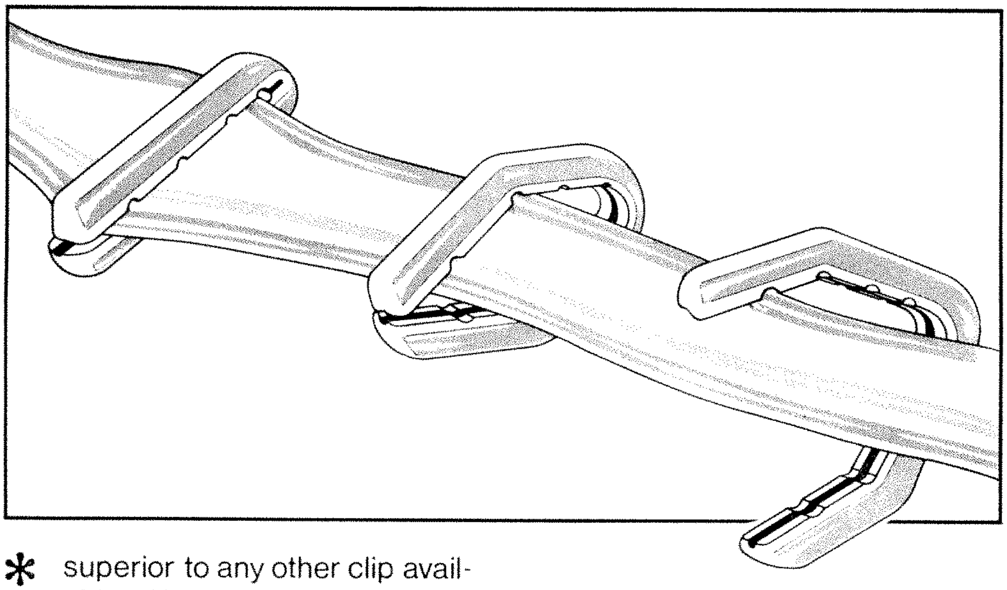

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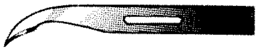

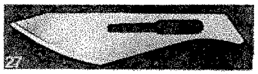
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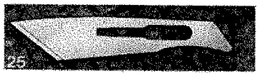
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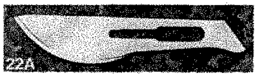
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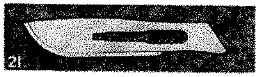
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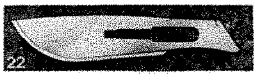
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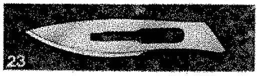
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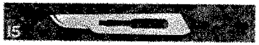
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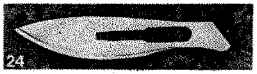
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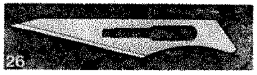
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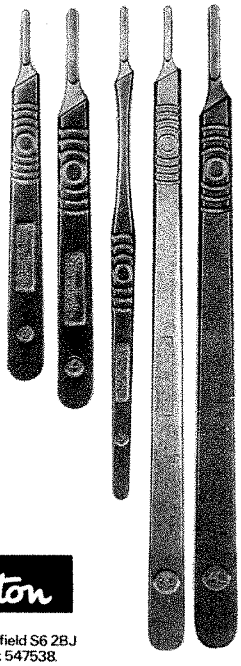

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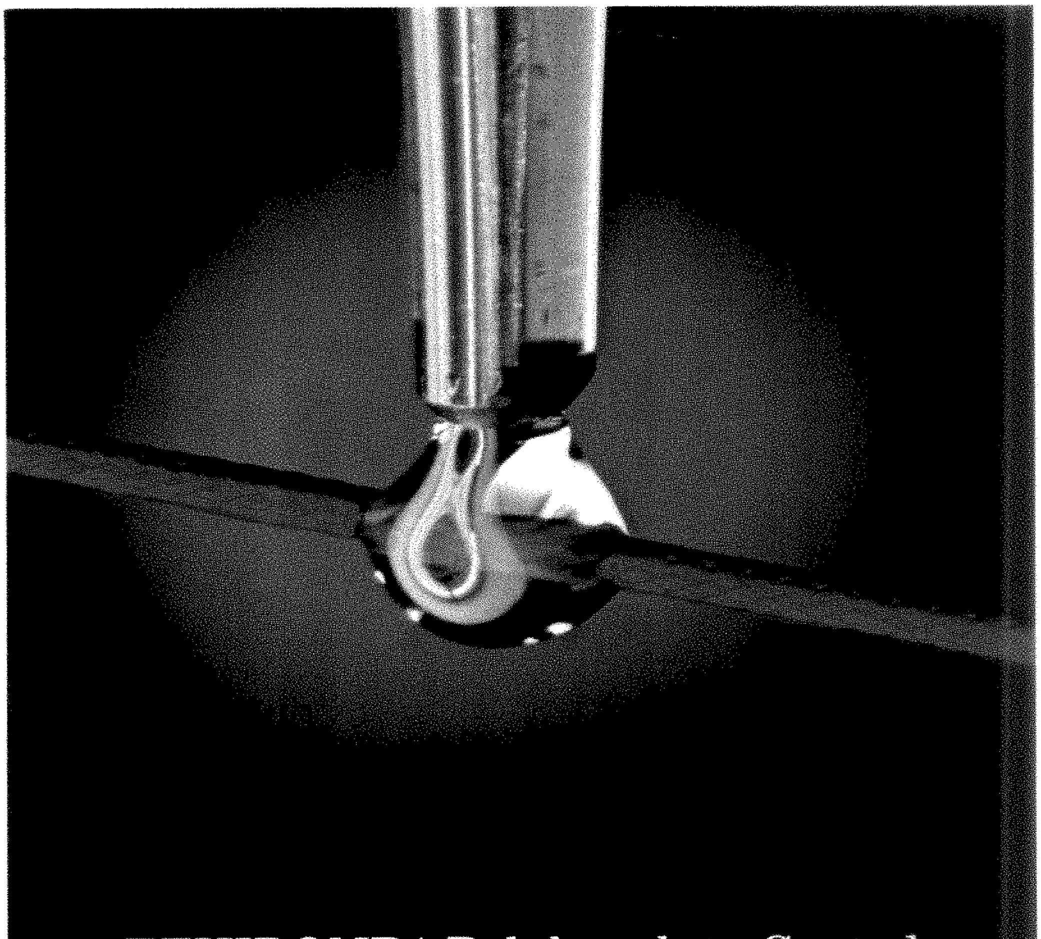

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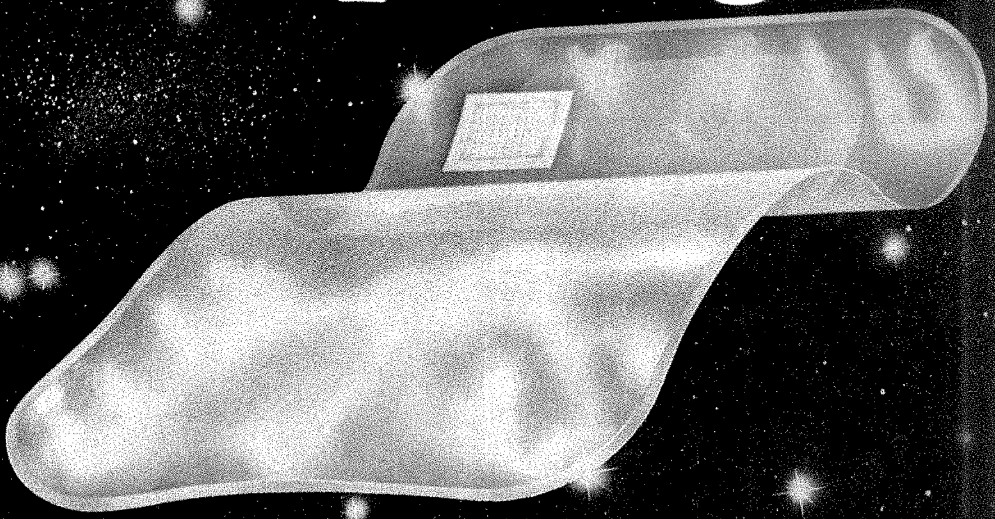

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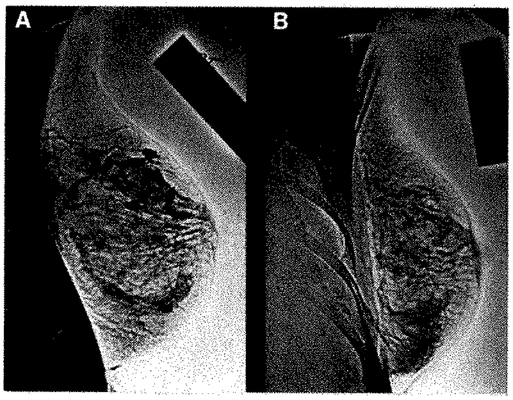
(Study of 58 patients given Danol for between 74 and 310 days. Am. J. Obstet. Gynec. 1977, 127: 130.)



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(Preliminary report on open study of 260 patients given Danol for 4 to 6 months. J. int. med. Res. 1977, 5 (Suppl. 3) 101-108.)

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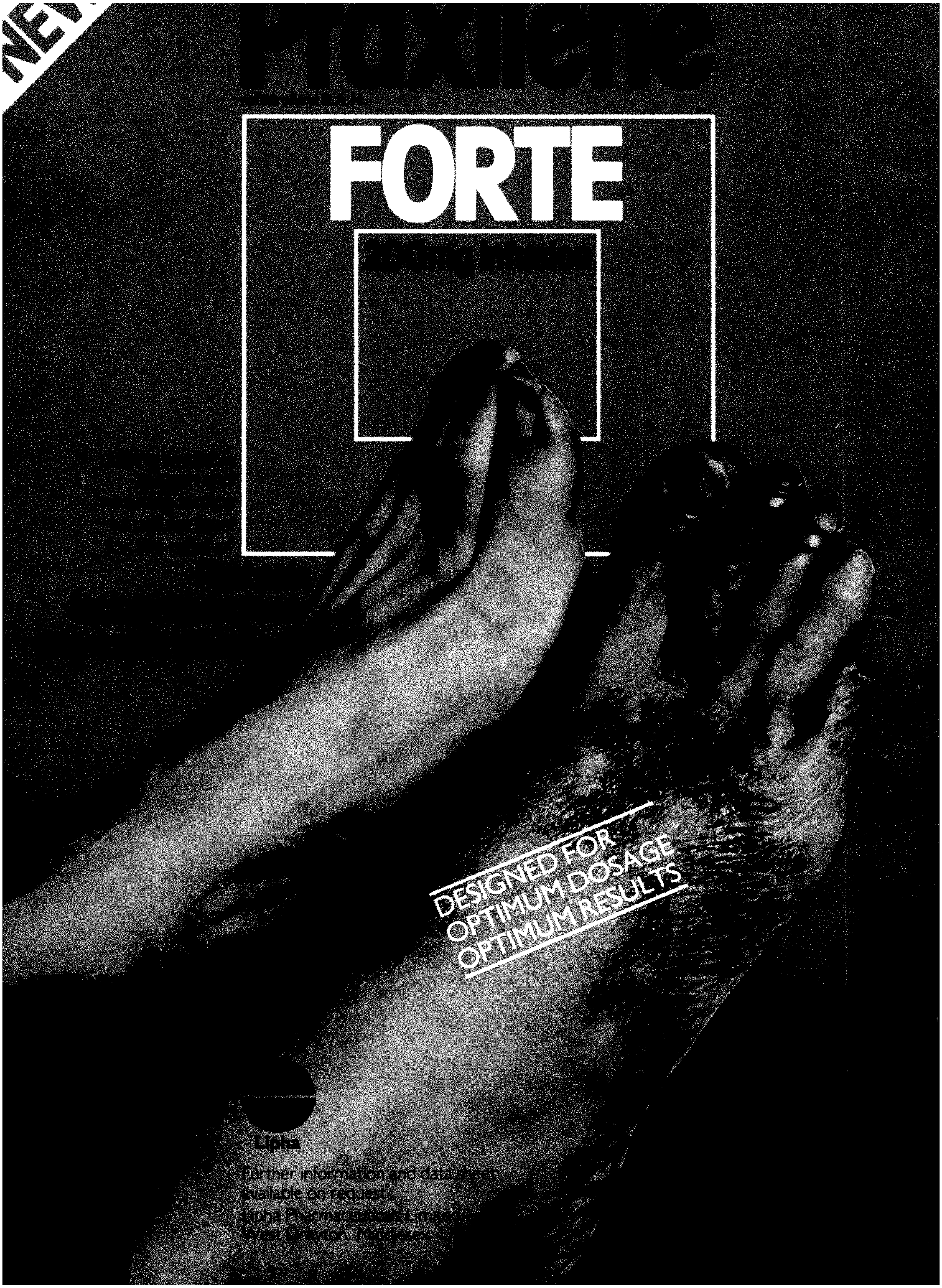

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Distribution of plasma-bound hydroxyproline in breast cancer, benign breast disease and healthy females

M. F. NEHLAWI, A. CUSCHIERI, J. CLARK AND R. A. B. WOOD[*]

SUMMARY

In normal adult females, patients with benign breast disease and patients with breast cancer, hydroxyproline (OHPro) was found in the plasma attached to the protein fractions which were separated by Sephadex gel filtration. In addition, a distinct moiety, probably a protein sub-unit, containing substantial amounts of this imino acid, occurred in between gel filtration fractions III and IV. Quantitative differences in the OHPro content of these various fractions were observed in the groups of patients studied. Significant elevations in the peptide-bound OHPro (fraction IV) were found only in patients with breast cancer and the level appeared to correlate with the degree of advancement of the disease. Similar findings relate to the OHPro content of the sub-protein moiety which is found between gel filtration fractions III and IV. A reduced level of high molecular weight hyproprotein (fraction I) was found in the breast cancer group.

URINARY hydroxyproline (OHPro) determination has been used as a sensitive index of collagen metabolism in human tissue (Prockop, 1963). Excretion of this imino acid is elevated in a number of disease states particularly in disorders of connective tissue, skin and the endocrine system (Ziff et al., 1956; Benoit et al., 1963; Brunish and Sørensen, 1965). An increased excretion of urinary OHPro is also encountered in primary and secondary tumours of bone (Platt et al., 1964). In 1973 Cuschieri reported that urinary OHPro was persistently elevated in patients with breast cancer who subsequently developed osseous deposits and this was later confirmed by Powles et al. (1975) and Roberts et al. (1975).

Plasma OHPro is found in the free and bound forms. The presence of dialysable OHPro-containing peptides in normal plasma has been previously reported (Prockop et al., 1962; Smiley and Ziff, 1964). In addition, there is a form of OHPro which is non-dialysable and protein-bound and which is released by acid or alkaline hydrolysis (Le Roy et al., 1964). The latter has been referred to as hyproprotein or collagen-like protein as it is resistant to hydrolysis by pronase and chymotrypsin. Increased levels of hyproprotein(s) have been reported in a variety of clinical states (Le Roy and Sjoerdsma, 1965). This study was undertaken to investigate the distribution of peptide- and protein-bound OHPro in the plasma of patients with benign breast disease and patients with early and advanced breast cancer.

Patients and methods

Included in the study were 32 patients with histologically proved breast cancer, 14 patients with benign breast disease (fibroadenosis, cystic mastopathy, fibroadenoma) and 24 adult healthy females who were the control group.

On the basis of our method of staging, the breast cancer group was subdivided into 15 with early disease (group A) and 17 with advanced cancer (group B). Patients in group A had no evidence of dissemination and either no histological axillary node involvement or a maximum of two lymph nodes involved. The advanced breast cancer group had either evidence of metastatic spread or advanced locoregional disease with extensive axillary node involvement, defined as three or more ipsilateral axillary nodes with tumour deposits on histological examination.

The assessment of patients with breast cancer included clinical examination, mammography, aspiration needle cytology with subsequent frozen-section histology, technetium-99^{m} sulphacolloid liver scan, liver function tests (serum albumin, total protein, bilirubin, alkaline phosphatase, aspartate transaminase, gamma-glutamyl transpeptidase and prothrombin time), laparoscopy, technetium-99^{m} methylene diphosphonate bone scan, chest X-ray and X-ray of the lumbosacral spine and pelvis. Hot areas on the isotope bone scan were further investigated by radiology, and areas of increased uptake of the isotope were interpreted as deposits only if the X-ray films of the region showed no evidence of benign disease or trauma.

Both patients and control subjects were put on a gelatin-free diet for 2 days. The blood samples for OHPro studies were taken at the end of this period. None of the patients or controls admitted to the study had any concurrent disease known to affect the turnover of collagen and the excretion of OHPro in the urine. Blood was collected in EDTA for the estimation of plasma OHPro. The plasma was separated and stored at −20 °C until required.

The procedure of Le Roy et al. (1964) was modified for the estimation of plasma-bound OHPro. One millilitre of plasma and 4·0 ml of ethanol were mixed and the solution was left to stand at room temperature for 15 min. It was then centrifuged at 2127 *g* for 10 min. The protein residue was separated from the ethanol layer.

To the protein precipitate, 2·0 ml 12 M HCl were added and the mixture was hydrolysed at 120 °C and 12 psi, for 18 h. The hydrolysate was evaporated to dryness and then dissolved in 1·5 ml of distilled water. One millilitre of the mixture was transferred to the cation-exchange chromatography column. The eluate solution was collected, neutralized, evaporated to dryness and then dissolved in 1·0 ml distilled water. Grant's method (1964) was used to measure OHPro.

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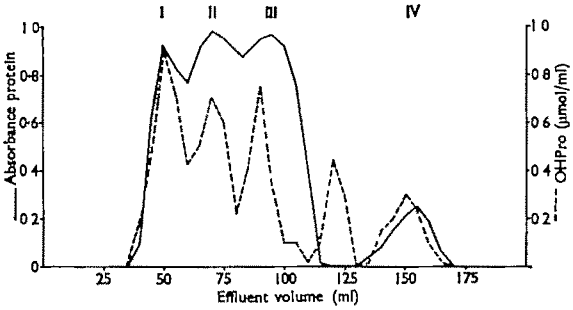

Fig. 1. Hydroxyproline (OHPro) in protein fractions from plasma of healthy female volunteers.

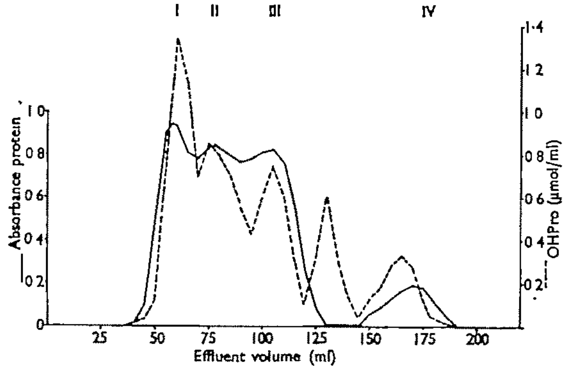

Fig. 2. Hydroxyproline (OHPro) in protein fractions from plasma of patients with early breast cancer (group A).

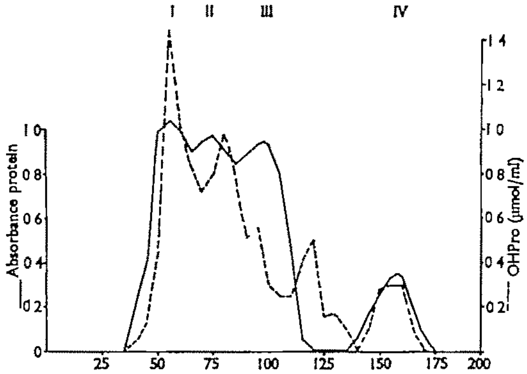

Fig. 3. Hydroxyproline (OHPro) in protein fractions from plasma of patients with advanced breast cancer (group B).

Plasma proteins were fractionated using a Sephadex G200 gel filtration. The column height was 90 cm and its diameter 1·5 cm. Four-millilitre plasma samples were run in a buffer containing 0·154 M NaCl and 0·01 M Tris at pH 8·0. Sodium azide (0·02 per cent) was added to the solution to avoid bacterial growth. A flow rate of 4·0 ml/h was adopted (bed volume, 135 ml). Fractions of 5·0 ml each were collected for about 36 h in an automated fraction collector (LKB). The proteins were measured by UV absorption at 280 nm. Two millilitres of 12 M HCl were added to 4·0 ml of each protein fraction, hydrolysis was then performed and this was followed by cation-exchange chromatography. The OHPro content of each fraction was then measured.

TABLE I: TOTAL BOUND PLASMA HYDROXY-PROLINE

Group	No.	Bound OHPro (μmol/l)
Healthy	24	138·2±1·18
Benign breast disease	14	134·4±3·15
Breast cancer group A	15	144·4±1·5*
Breast cancer group B	17	159·9±2·16*

($\bar{X}$±s.e. mean.)
* $P<0·05$ (rank sum test).

TABLE II: PERCENTAGE PROTEIN IN GEL FILTRATION FRACTIONS

Group	No.	Fraction I	Fraction II
Healthy females	14	23·9±0·96	34·5±1·60
Benign breast disease	10	27·5±0·81**	38·7±2·58
Breast cancer			
Group A	15	29·5±1·18**	31·9±1·53
Group B	17	26·5±1·26	35·5±1·07

		Fraction III	Fraction IV
Healthy females	14	31·8±1·42	9·2±0·80
Benign breast disease	10	24·8±2·16*	8·1±0·35
Breast cancer			
Group A	15	28·3±1·76*	9·0±1·01
Group B	17	28·9±1·79*	8·2±0·96

($\bar{X}$±s.e. mean.)
* $P<0·05$; ** $P<0·01$ (rank sum test).

Statistical analysis

As the data obtained were not of a normal distribution, all statistical comparisons were carried out by non-parametric analysis using the rank sum test.

Results

The total bound OHPro (peptide and protein) in the plasma (*Table I*) was significantly elevated in patients with breast cancer compared with healthy controls and patients with benign breast disease. In general, the high levels were obtained in patients with advanced disease (group B). However, the wide scatter of these results did not allow any effective discrimination between breast cancer and the other groups.

The protein content of the various gel filtration fractions is shown in *Table II*. Minor differences from control values were found in both patients with benign breast disease and patients with breast cancer but there was considerable overlap between the various groups. Small but significant elevations of the protein content of fraction I were observed in both patients with benign breast disease and patients with early breast cancer (group A). A reduced protein content of fraction III was found in patients with breast cancer but a greater reduction was observed in the protein content of the same fraction in patients with benign breast disease.

Typical examples of the plasma protein separation patterns and the OHPro content of the various fractions in healthy females, group A and group B breast cancer patients are shown in *Figs*. 1, 2 and 3. The peaks of OHPro and the protein fractions were coincident. However, an additional OHPro peak was found located in between gel filtration fractions III and IV. There was no qualitative difference in either the protein separation or the distribution of OHPro between the various groups. The OHPro content of the various gel filtration fractions is shown in *Table III*.

Table III: HYDROXYPROLINE (μmol/l) IN GEL FILTRATION FRACTIONS

Group	No.	Fraction I	Fraction II	Fraction III	Separate OHPro peak between fractions III and IV	Fraction IV
Healthy females	14	51·1±3·29	36·8±2·20	27·9±1·66	5·4±1·02	15·0±2·43
Benign breast disease	10	49·7±5·12	30·3±1·84	21·2±1·80	10·6±2·40	17·3±4·63
Breast cancer						
Group A	15	40·4±2·80*	35·1±2·34	29·4±3·24	14·1±2·40**	26·9±2·86*
Group B	17	40·9±2·62*	37·1±1·98	33·6±1·55	18·6±1·60**	29·7±2 19**

$\bar{X}$ ±s.e. mean).
* $P<0{\cdot}05$; ** $P<0{\cdot}01$ (rank sum test).

Table IV: HYDROXYPROLINE SPECIFIC ACTIVITY IN GEL FILTRATION FRACTIONS

Group	No.	Fraction I	Fraction II	Fraction III	Fraction IV
Healthy females	14	2·85±0·15	1·61±0·13	1·31±0·08	2 02±0·25
Benign breast disease	10	2·60±0 16	1·17±0 07*	1·17±0·06	2·12±0·65
Breast cancer					
Group A	15	2·07±0 08**	1·65±0·09	1·56±0·16	4·04±0·52**
Group B	17	2·27±0 09**	1·52±0·08	1·80±0·18*	5·60±0·62**

($\bar{X}$±s.e. mean.)
* $P<0{\cdot}025$; ** $P<0\ 005$ (rank sum test).

A marked elevation of the OHPro content of fraction IV (peptide fraction) was observed in patients with breast cancer. The level of this peptide-bound plasma OHPro clearly separated the breast cancer patients from both patients with benign disease and healthy female controls. In addition, the OHPro peak between gel filtration fractions III and IV was significantly elevated only in patients with breast cancer. The OHPro content of both fraction IV and the separate OHPro peak in between fractions III and IV appeared to relate with degree of advancement of the disease. A significant reduction of the OHPro content of fraction I was found in patients with cancer of the breast.

As there were quantitative variations of protein in the various fractions, the specific activity of OHPro in each gel filtration fraction was calculated and expressed as mmol OHPro/g protein. These results are shown in *Table IV* and demonstrate a significant elevation of the specific activity of OHPro in fraction IV and a decreased specific activity in fraction I in patients with cancer of the breast.

Discussion

In addition to the free imino acid, OHPro is found in the human plasma in the peptide-bound form and as a component of certain proteins known as hyproproteins. The high molecular weight hyproprotein which accounts for 55 per cent of the total is eluted from Sephadex columns with the early protein fractions containing the α2-macroglobulins and α- and β-lipoproteins. A smaller later peak of hyproprotein has been recovered from the albumin fraction (Le Roy et al., 1964).

Although the total bound OHPro in the plasma was found to be elevated in patients with breast cancer, there was considerable overlap between the groups studied, including the healthy female controls. There were no qualitative differences from the normal pattern of distribution of OHPro amongst the plasma protein fractions in patients with either benign breast disease or breast cancer.

One of the significant quantitative changes from the normal observed in the breast cancer patients was a reduction of the high molecular weight hyproprotein in fraction I, despite the elevation of the total protein content of this fraction from the plasma of patients with breast cancer. The interpretation of this finding is difficult as both the exact nature and the pathological significance of hyproproteins remain to be determined. The suggestion that they represent collagen released from cells (Le Roy et al., 1964, 1965; Oh et al., 1968) is based on indirect evidence and the chemical identity between hyproprotein(s) and collagen has not been established. Even if they are associated with the metabolism of collagen, hyproproteins constitute a different pool from the peptide-bound OHPro as Le Roy et al. (1965) reported a total lack of correlation between hyproprotein levels and urinary peptide OHPro. Elevated levels of plasma hyproprotein have been found in the acute phase of a variety of disease states such as inflammatory and febrile illnesses, renal disease, rheumatoid arthritis etc. It could be argued that plasma hyproproteins are acute phase reactants akin to C-reactive protein, haptoglobin and pre-albumin. There is some evidence based on animal experiments with C^{14}-proline and a positive correlation between hyproprotein content and IgM levels in humans that the high molecular weight hyproprotein contains the immunoglobulin IgM (Tomaszewski and Kowalewski, 1975).

The plasma peptide-bound OHPro has received very little attention. It accounts for 6–10 per cent of the total OHPro in the plasma of healthy adults. Isotopic studies have shown that peptide-bound OHPro in the urine is derived from the turnover and degradation of both soluble and insoluble collagen (Prockop, 1963). In the present study, a significant elevation of the OHPro content of fraction IV was found only in patients with breast cancer. This gel filtration fraction reflects the polypeptide component of the plasma and its OHPro content is, therefore, in the peptide-bound form. Patients with extensive locoregional disease and/or evidence of spread tended to have higher levels than patients with early breast cancer although there was overlap between these two subgroups. As it is extremely likely that some of the patients assessed as having early disease will have occult spread despite attempts at accurate staging, a valid assessment on the value of plasma peptide-bound OHPro as a prognostic index and as a monitor of disease activity in cancer of the breast can only be based on the subsequent clinical outcome of these patients. We have as yet no definite information on any relation between plasma peptide-bound OHPro and survival in breast cancer as the period of follow-up for the patients included in this study has ranged from 6 months to 2 years.

A distinct peak of OHPro was observed in between gel filtration fractions III and IV. This is likely to represent a protein sub-unit rich in OHPro. A significant increase in this OHPro peak was found in cancer of the breast, especially in patients with advanced disease. Further studies including purification, degradation and high pressure liquid chromatography are being performed in our laboratory to determine the exact nature of this moiety.

Whilst some of the changes reported in this study may simply reflect an increased turnover of collagen by metastatic tumour, their protein nature cannot be fully explained by this simple hypothesis. It seems logical to assume that the increased collagen turnover is not a local tissue response, but a component of a systemic reaction to an advancing neoplastic process characterized by complex changes in the plasma proteins. There is some support for this concept from recent studies in lymphoma patients where an increased excretion of urinary peptide OHPro was found exclusively in patients with systemic manifestations and related closely with pyrexia, elevated ESR and weight loss (Nehlawi et al., 1979).

Acknowledgement

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References

BENOIT F. L., THEIL G. B. and WATTEN R. H. (1963) Hydroxyproline excretion in endocrine disease. *Metabolism* **12**, 1072–1082.

BRUNISH R. and SØRENSEN B. (1965) Urinary excretion of acid mucopolysaccharides and hydroxyproline in psoriasis. *Dermatologica* (*Basel*) **130**, 165–172.

CUSCHIERI A. (1973) Urinary hydroxyproline excretion in early and advanced breast cancer: a sequential study. *Br. J. Surg.* **60**, 800–803.

GRANT R. A. (1964) Estimation of hydroxyproline by the auto analyser. *J. Clin. Pathol.* **17**, 685–686.

LE ROY E. C., KAPLAN A., UDENFRIEND S. et al. (1964) A hydroxyproline-containing, collagen-like protein in plasma and a procedure for its assay. *J. Biol. Chem.* **239**, 3350–3356.

LE ROY E. C. and SJOERDSMA A. (1965) Clinical significance of a hydroxyproline-containing protein in human plasma. *J. Clin. Invest.* **44**, 914–919.

NEHLAWI M. F., SHAW D., MITCHELL P. E. G. et al. (1979) Urinary hydroxyproline excretion in patients with Hodgkin's disease and non-Hodgkin's lymphoma. *Clin. Oncol.* (In the press.)

OH S. I., NEFF B. J. and BLOCK W. D. (1968) Soluble collagen in human serum. *Clin. Chim. Acta* **21**, 1–8.

PLATT W. D., DOOLITTLE L. H. and HARTSHORN J. W. S. (1964) Urinary hydroxyproline excretion in metastatic cancer. *N. Engl. J. Med.* **271**, 287–290.

POWLES T. J., LEESE C. L. and BONDY P. K. (1975) Hydroxyproline excretion in patients with breast cancer and response to treatment. *Br. Med. J.* **2**, 164–166.

PROCKOP D. J. (1963) Isotopic studies on collagen degradation and the urine excretion of hydroxyproline. *J. Clin. Invest.* **43**, 453–460.

PROCKOP D. J., KEISER H. R. and SJOERDSMA A. (1962) Gastrointestinal absorption and renal excretion of hydroxyproline peptides. *Lancet* **2**, 527–528.

ROBERTS J. G., WILLIAMS M. and HENK H. M. (1975) The hypronosticon test in breast cancer. *Clin. Oncol.* **1**, 33–43.

SMILEY J. D. and ZIFF M. (1964) Urinary hydroxyproline excretion and growth. *Physiol. Rev.* **44**, 30–44.

TOMASZEWSKI J. and KOWALEWSKI J. (1975) High-molecular-weight hydroxyproline protein in relation to immunoglobulins M (IgM) in human blood serum. *Clin. Chim. Acta* **60**, 185–189.

ZIFF M., KIBRICK A., DRESNER E. et al. (1956) Excretion of hydroxyproline in patients with rheumatic and nonrheumatic diseases. *J. Clin. Invest.* **35**, 579–587.

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Midline cancer of the floor of the mouth: role of suprahyoid dissection

ALI A. EL-DOMEIRI*

SUMMARY

Of 37 patients with squamous cell carcinoma of the floor of the mouth seen during a 5-year period, 28 were treated primarily by surgery. Ten of the 28 patients presented with midline cancers measuring between 1·0 and 3 cm (T_1 and T_2). Three of these patients had local excision only. Metastases to the submandibular lymph nodes later occurred in 1 of these 3 patients. The remaining 7 patients with midline lesions had wide excision of the tumour, marginal resection of the mandible and bilateral suprahyoid node dissection. Of these 7 patients 4 remained free of disease for periods ranging between 2 and 5 years. Two of these had lymph node metastases. These results suggest that en bloc excision of relatively small midline cancers (i.e. not exceeding 2 cm (T_1) in largest diameter) with bilateral suprahyoid node dissection gives effective control of these lesions.

SQUAMOUS cell carcinoma of the floor of the mouth arises from a strip of mucosa lining a U-shaped groove between the tongue and alveolar margin. This tumour spreads directly to adjacent structures and, via the lymphatics, to the cervical lymph nodes (Helfrich et al., 1972). Distant metastases are less frequent and occur later. Cancers originating in the anterior part of the floor of the mouth frequently extend across the midline, and hence have the potential to metastasize bilaterally to the regional lymph nodes (Ditrois, 1972). Furthermore these lesions often involve the orifices of Wharton's ducts, which may act as conduits for tumour extension to the submandibular region (Landa and Zarem, 1973).

Patients with cancer of the floor of the mouth who were included in this study were treated primarily by surgery. A conservative surgical approach was adopted in patients with relatively small lesions that originated in the midline and involved both sides of the floor of the mouth.

Patients and methods

Patients

During a 5-year period, 1971–5, a total of 37 patients with squamous cell carcinoma of the floor of the mouth was treated at the University of Illinois and Cook County Hospitals. Thirty-two of these patients were male and 5 female, with ages ranging between 44 and 79 years. Sixteen patients presented with anterior lesions that crossed the midline (*Table I*). Of these 16 patients, 10 with tumours measuring 1–3 cm (T_1 and T_2) which seemed to originate in the midline and involved both sides were considered candidates for a conservative operation. Two of the 10 patients had palpable nodes in the suprahyoid region and 3 presented with unilateral or bilateral swollen submandibular salivary glands.

Methods

Three patients with superficial midline cancers not exceeding 1·5 cm in diameter (T_1) and who had no palpable lymph nodes in the neck were treated by wide local excision through the open mouth. The defect was closed primarily by mobilizing the adjacent mucosa or by split-thickness skin graft.

Table I: STAGE AND LOCATION OF TUMOUR

Stage	Total no.	Crossing midline	Lateral
I (T_1, N_0, M_0)	7	6	1
II (T_2, N_0, M_0)	6	2	4
III (T_3, N_0, M_0; *T_x, N_1, M_0)	11	4	7
IV (T_x, N_{2-3}, M_0; T_x, †N_x, M_1)	13	4	9
Total	37	16	21

* $T_x = T_1$, T_2 or T_3.
† $N_x = N_0$, N_1, N_2 or N_3.

The other 7 patients, with early midline cancers measuring 1·5–3 cm in diameter, had excision of the anterior floor of the mouth, marginal resection of the mandible and bilateral suprahyoid node dissection. A midline lower lip-splitting incision that was extended bilaterally into the submandibular region was utilized (*Figs*. 1–3). Closure of the surgical defect was achieved by mobilizing the mucosa of the lip, cheek and tongue. In 2 patients a second operation was carried out to release the tongue and widen the labiolingual gutter to accommodate a dental prosthesis. In these instances a split-thickness skin graft was used to cover the raw area in the floor of the mouth.

Histological examination of the specimens from each patient revealed that the margins of resection were free of cancer. Of the 7 patients who underwent suprahyoid node dissection, 4 had metastases to the lymph nodes. The number of involved nodes in these patients ranged between 1 and 3.

Treatment of the remaining 27 patients seen during this 5-year period with cancer of the floor of the mouth is shown in *Table II*. Seven patients with advanced disease received radiation therapy or chemotherapy or both. Eighteen patients with lesions confined to one side of the floor of the mouth were treated by resection of the floor of the mouth, part of the mandible and ipsilateral radical neck dissection. Of these 18 patients, 6 with stage III or IV disease received preoperative radiation therapy (5000 rad in 5 weeks). Two other patients with operable tumours were treated by radiation therapy only.

Results

All patients were followed for a minimum period of 2 years (*Table III*). One of the 3 patients who had local excision developed metastases in the submandibular lymph nodes. The other 2 remained free of disease but had persistent swelling of the submandibular salivary glands. These 2 patients had suprahyoid node dissection later in the course of follow-up, mainly to remove the swollen, functionless salivary glands: in neither patient did the removed lymph nodes show metastases. Of the 7 patients who had wide excision of the tumor and suprahyoid node dissection, 4 with T_1 lesions (stage I or III) were free of disease at 2 years. Two of these 4 patients, 1 without clinically palpable nodes, i.e. stage I, and 1 with palpable nodes, i.e. stage III, had histologically proved metastases to lymph nodes in the resected specimen. Recurrent disease developed in the remaining 3 patients who had T_2 lesions (stages II and III). Two patients had local recurrence in the oral cavity and 1 had recurrent disease in the mouth and upper cervical lymph nodes

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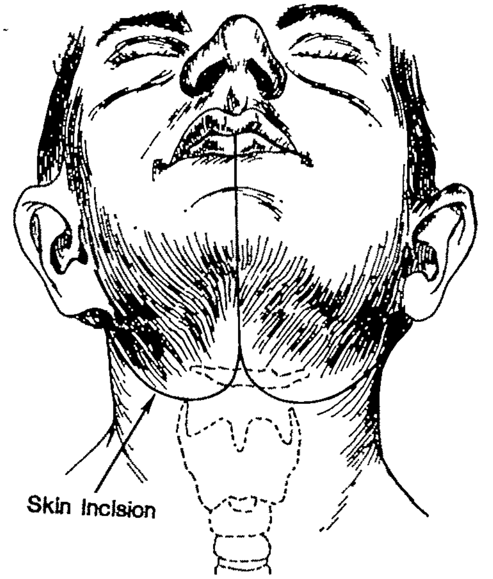

Fig. 1. Midline lip-splitting incision extending bilaterally to the mastoid process.

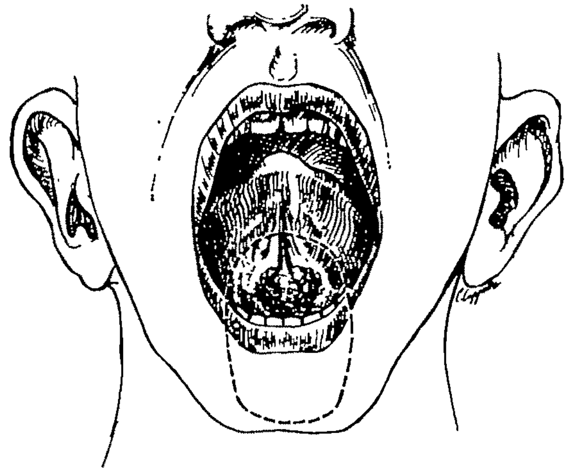

Fig. 2. Extent of resection of a small tumour outlined in this figure.

on one side. One of these 3 patients who received preoperative radiation therapy failed to respond to additional postoperative radiation therapy and chemotherapy. This patient died of the tumour in less than 1 year. The other 2 patients were living with disease during the period of follow-up. Both these patients received radiation therapy and/or chemotherapy. In a comparable group of 11 patients with T_1 and T_2 tumours confined to one side of the floor of the mouth, and who were treated by a resection of the floor of the mouth and the mandible combined with ipsilateral neck dissection (commando operation), 6 were free of disease at 2 years.

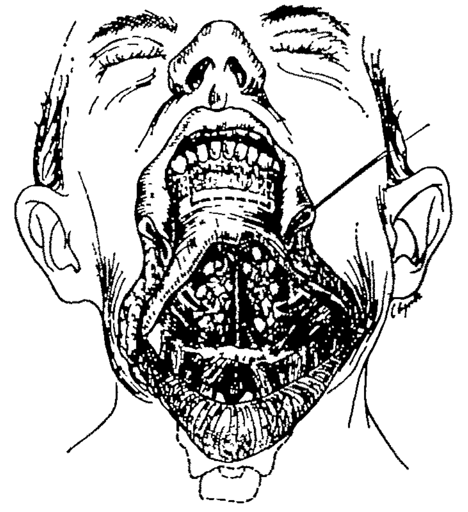

Fig. 3. Extent of node dissection: submandibular gland and lymph nodes are mobilized medially on both sides. This tissue is left attached to the submental region to be removed *en bloc* with the lesion in the floor of the mouth. Dotted line shows extent of bone resection.

Table II: DEFINITIVE TREATMENT IN 37 PATIENTS

Stage	Excision of primary: No node dissection	Excision of primary: Suprahyoid dissection	Excision of primary: Radical neck dissection	Radiation therapy	Radiation and chemotherapy
I ($n=7$)	3	3	1	0	0
II ($n=6$)	0	2	2	2	0
III ($n=11$)	0	2 (1*)	9 (2*)	0	0
IV ($n=13$)	0	0	6 (4*)	4	3
Total ($n=37$)	3	7	18	6	3

* Received preoperative radiation therapy.

Table III: RESULTS OF SURGICAL TREATMENT IN 28 PATIENTS (AT 2 YEARS)

Stage	Local excision		Excision and suprahyoid dissection		Excision and radical neck dissection	
	Total	NED >2 yr	Total	NED >2 yr	Total	NED >2 yr
I ($n=7$)	3	2	3	3	1	1
II ($n=4$)	0	0	2	0	2	1
III ($n=11$)	0	0	2	1*	9	5
IV ($n=6$)	0	0	0	0	6	2
Total ($n=28$)	3	2	7	4	18†	9

* T_1, N_1, M_0.

† Eleven had lateral lesions (T_1 or T_2) of whom 6 were free of disease at 2 years.

NED, no evidence of disease.

Discussion

The chances of curing early cancer of the oral cavity by surgery or irradiation are comparable. In patients with carcinoma of the floor of the mouth control can be achieved with either therapy as initial treatment in two-thirds of patients with stage I and II disease (Flynn et al., 1973). In our series patients with early lesions were treated primarily by surgery. The choice of treatment was influenced by the fact that a large number of these patients were heavy consumers of tobacco and alcohol and exhibited signs of chronic irritation of the oral mucosa. A number of reports indicate that such patients have a greater incidence of oral cancer and are at high risk of developing a second primary (Wynder et al., 1957; Johnston and Ballantyne, 1977). Radiation therapy could possibly increase the carcinogenic effect in these persons (Barton, 1971). Also, cancers of the floor of the mouth frequently involve the alveolar margin and are hidden by the mandible. Radical radiotherapy for these lesions is associated with a significant incidence of osteoradionecrosis (Montana et al., 1969; Hardingham et al., 1977). The incidence of bone necrosis has been reported as notably higher in patients with cancers of the floor of the mouth than in those with other tumours of the oral cavity (Silverman and Chierici, 1965; Barton, 1971).

Approximately 72 per cent of all cancers of the floor of the mouth are found in the anterior part of the gingivolingual sulcus (Mashberg and Meyers, 1976). A significant number of these tumours (29 per cent) have crossed the midline at the time of initial presentation (Helfrich et al., 1972). The incidence of cancers that originated in the midline and equally involved both sides, however, was 7 per cent. Because cancer involving the midline can metastasize bilaterally (Ditrois, 1972; Landa and Zarem, 1973), effective control of these tumours entails eradication of the disease at the primary site and in the vulnerable lymph nodes on both sides of the neck.

The presence of clinically positive nodes or the presence of a lesion whose excision requires a surgical approach that enters the neck are generally accepted criteria for performing radical neck dissection (Harrold, 1971; Spiro and Strong, 1973). The extent of the procedure, with its attendant complications, as well as the low yield of histologically positive nodes in patients who do not have clinically palpable disease, weighs against elective *radical* neck dissection. In this series, suprahyoid node dissection, being an operation of considerably lesser magnitude, was used in the treatment of early midline cancers (T_1 and T_2) to secure a wider margin of resection and remove the lymph nodes and salivary glands that are sites for regional metastases on both sides of the neck. The procedure did not contribute to any significant increase in morbidity or mortality and produced excellent cosmetic and functional results. Marginal resection of the bone preserved the continuity of the mandibular arch and eliminated the disabling deformity that followed removal of the anterior segment of the mandible.

The overall results in patients with midline lesions who had suprahyoid node dissection compared favourably with the results in patients having early lateral lesions treated by a combined resection of the floor of the mouth and ipsilateral neck dissection. Four of 7 patients in the former group and 6 of 11 in the latter group were free of disease at 2 years. The conservative surgical approach for midline lesions was particularly effective in controlling tumours measuring 2 cm or less in diameter (T_1). Also, there were indications that the procedure could have benefited patients with small superficial lesions who were treated by local excision only. In 1 of these 3 patients metastases developed to the submandibular lymph nodes. However, failure of this conservative approach to cure patients with tumours larger than 2 cm indicates that a more radical excision or a combination of therapies should be considered in the treatment of these patients (Leonard and Hass, 1970). Preoperative radiation therapy has been most commonly used as an adjunct to radical surgery, the purpose of irradiation being to eradicate microscopic nests of cells existing beyond the margins of resection, as well as to reduce the bulk of the tumour.

Effective palliation of advanced and recurrent cancers in the anterior floor of the mouth has been accomplished by a combination of chemotherapy and high doses of radiation therapy. Tumours located in the anterior part of the floor of the mouth in particular are more accessible to treatment by intra-arterial chemotherapy infusion (El-Domeiri and Chaudhuri, 1975). A significant reduction of the tumour mass and alleviation of symptoms occurred in some of the patients thus treated.

Acknowledgement

I wish to thank Mrs Laurie Barbour for her help in accumulating data on these patients.

References

BARTON R. T. (1971) Surgical treatment of carcinoma of the floor of the mouth. *Surg. Gynecol. Obstet.* **133**, 971–972.

DITROIS J. F. (1972) Nodal metastases and prognosis in carcinoma of the oral cavity. *Otolaryngol. Clin. North Am.* **5**, 333–342.

EL-DOMEIRI A. A. and CHAUDHURI P. (1975) Management of oral and pharyngeal cancer: a multidisciplinary approach. *Surg. Clin. North Am.* **55**, 107–115.

FLYNN M. B., MULLINS F. X. and MOORE C. (1973) Selection of treatment in squamous carcinoma of the floor of the mouth. *Am. J. Surg.* **126**, 477–481.

HARDINGHAM M., DALLEY V. M. and SHAW H. J. (1977) Cancer of the floor of the mouth: clinical features and results of treatment. *Clin. Oncol*, **3**, 227–246.

HARROLD C. C. jun. (1971) Management of the floor of the mouth. *Am. J. Surg.* **122**, 487–493.

HELFRICH G. B., NICKELS M. E., EL-DOMEIRI A. A. et al. (1972) Management of cancer of the floor of the mouth. *Am. J. Surg.* **124**, 559–562.

JOHNSTON W. D. and BALLANTYNE A. J. (1977) Prognostic effect of tobacco and alcohol use in patients with oral tongue cancer. *Am. J. Surg.* **134**, 444–447.

LANDA S. J. F. and ZAREM H. A. (1973) Cancer of the floor of the mouth and the gingiva. *Surg. Clin. North Am.* **53**, 135–145.

LEONARD J. R. and HASS A. C. (1970) Management of cancer of the oral cavity: the trend toward combined radiotherapy and surgery. *Am. J. Surg.* **120**, 514–521.

MASHBERG A. and MEYERS H. (1976) Anatomical site and size of 222 early asymptomatic oral squamous cell carcinomas: a continuing prospective study of oral cancer, II. *Cancer* **37**, 2149–2157.

MONTANA G. S., HELLMAN S., VON ESSEN C. F. et al. (1969) Carcinoma of the tongue and floor of the mouth. *Cancer* **23**, 1284–1289.

SILVERMAN S. and CHIERICI G. (1965) Radiation therapy of oral carcinoma. *J. Periodont. Res.* **36**, 478–484.

SPIRO R. H. and STRONG E. W. (1973) Epidermoid carcinoma of the oral cavity and oropharynx. *Arch. Surg.* **107**, 382–384.

WYNDER E. L., BROSS I. J. and FELDMAN R. M. (1957) A study of the etiological factors in cancer of the mouth. *Cancer* **10**, 1300–1323.

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Phaeochromocytomas in 72 patients: clinical and diagnostic features, treatment and long term results

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SUMMARY

Phaeochromocytomas were diagnosed in 72 patients in Hammersmith, Belfast and Newcastle between 1955 and 1976. Fourteen were found unexpectedly at autopsy while 58 were diagnosed in life. Associated lesions included neurofibromatosis (7 patients), medullary carcinoma of the thyroid (3), renal artery stenosis (2) and cerebellar haemangioblastoma (1). The clinical features were similar to those reported by others. Hypertension was found in all but one of the patients and was sustained only in 17 per cent, paroxysmal only in 48 per cent and sustained with superadded paroxysms in 33 per cent. Hypertension was significantly greater in the women than in the men.

Diagnosis was confirmed chemically in all patients and urinary vanylmandelic acid (VMA) was elevated in all but one. Tumours were localized correctly by various radiographic techniques and by selective venous sampling in over 80 per cent of patients. The tumours were in adrenals in 59 patients (bilateral in 6) and at extra-adrenal, intra-abdominal sites in 13.

The tumours were removed surgically from those in whom they were diagnosed in life. Before 1967 3 of 17 patients died after operation (18 per cent). Since then patients have been prepared with alpha blockade and have received infusions of plasma, blood or dextran after removal of the tumours. One of 41 patients so treated has died after operation (2 per cent). Phaeochromocytomas were diagnosed and treated in pregnancy in 4 patients, all of whom survived. Two of the fetuses died.

Five tumours diagnosed in life were malignant and 2 recurred (40 per cent). Fifty-three were benign and 2 of these recurred locally (4 per cent).

All but 2 patients (who could not be traced) were followed completely from 1 to 20 years after operation and 3 died during this period. Two-thirds of the patients were alive after 10 years.

Paroxysmal hypertension was abolished by operation, but sustained hypertension often persisted and required drug therapy.

It is concluded that at least one-third of phaeochromocytomas are not diagnosed in life and that a high index of suspicion is required to bring them to light. If they are diagnosed and treated by present methods, the prognosis is good.

IN 1886 Fränkel first described a type of tumour for which Pick (1912) proposed the name phaeochromocytoma. The first complete study of a patient, in whom the diagnosis was made post mortem, was published by L'abbé, Tinel and Doumer in 1922. Four years later Vaquez and Donzelot (1926) recognized the condition during life, and Laubry (1927) treated the same patient with success (at least for 6 months) by irradiation of the adrenals. The first curative surgical removal of a phaeochromocytoma, which had not been diagnosed preoperatively, was reported by C. H. Mayo in 1927. Pincoffs (1929) was the first to recognize the condition preoperatively and then to cure the patient by removal of the tumour. Beer, King and Prinzmetal (1937) first isolated a pressor substance from the blood in such a patient and found that operation abolished the pressor effect. Phaeochromocytomas are now known to secrete adrenaline and noradrenaline in varying proportions (Holton, 1949).

The tumour is rare, but by 1951 Graham was able to review 207 patients from the world literature, and in the past decade several sizeable series have been reported (Sander et al., 1971—21 patients; Öhman et al., 1974—20 patients; ReMine et al., 1974—138 patients; Scott et al., 1976—44 patients; Melicow, 1977—100 patients). In recent years the diagnostic accuracy, localization and treatment have improved greatly (Harrison et al., 1975; Montgomery and Welbourn, 1975; Manger and Gifford, 1977). The long term results of treatment have received little attention and have been reported in only one large series (ReMine et al., 1974). Four of 138 patients died at operation and 128 of the survivors were followed for from 1 to 24 years. Of these, 96 per cent with benign tumours and 44 per cent with malignant lesions survived for 5 years.

The present review concerns a series of 72 patients, seen in three centres, all but two of whom were followed regularly until they died or until the end of the review period, that is from 1 to 20 years. Since many patients with phaeochromocytomas die before they are known to harbour tumours, a special effort was made to discover and include patients in whom the diagnosis was made for the first time at autopsy. Attention has been paid to presenting features, methods of diagnosis and localization, associated conditions, long-term results in patients subjected to operation and analyses of the effects of treatment on survival and on the blood pressure.

Patients

The series includes all patients with tumours diagnosed histologically as phaeochromocytomas in Hammersmith Hospital (in the years 1966–76), the Royal Victoria and City Hospitals, Belfast (1960–75), and the Royal Victoria Infirmary, Newcastle upon Tyne (1955–75). A detailed review of the records and of all surviving patients was made in 1976 and 1977.

The distribution of patients by centre and by whether the tumour was obtained at operation or at autopsy is shown in *Table I*. The numbers in each centre were similar. Fourteen tumours (19 per cent) were found incidentally after death, the highest proportion (35 per cent) being in Belfast.

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Clinical features

General: There were 40 male and 32 female patients (*Table I*). The ages at diagnosis were distributed normally (*Table II*), all but 13 patients being between the ages of 20 and 60 years. The youngest was a girl of 9 and the oldest a man of 82.

The duration of symptoms shows a skew distribution (*Table III*), nearly half the patients having a history of less than 1 year at the time of diagnosis. In those whose tumours were found at autopsy the data are inevitably less accurate than in those whose lesions were diagnosed in life. The longest history was 20 years.

No patient gave a family history of phaeochromocytoma.

Twenty major lesions, in addition to phaeochromocytoma, were found in 18 of the patients (*Table IV*). Neurofibromatosis, (10 per cent) (Glushien et al., 1953), medullary carcinoma of the thyroid (Sipple's syndrome, multiple endocrine adenopathy type II) (4 per cent) (Harrison and Thompson, 1975), renal artery stenosis (shown on arteriography on the same side as the tumours) (Melicow, 1977) and cerebellar haemangioblastoma (Chapman and Diaz-Perez, 1962) have all been reported frequently before, but the other conditions (with the possible exception of duodenal ulcer, q.v.) were probably associated by chance.

Patients diagnosed in life: The presenting features in the 58 patients were variable and similar to those reported in other series (*Table V*). Two patients had had previous operations for phaeochromocytomas elsewhere and were referred with local recurrences of their tumours.

Hypertension: A patient was defined as hypertensive if (*a*) the mean of all the systolic or diastolic readings, other than those obtained during hypertensive crises, was greater than the mean for subjects of the same sex and age in the general population (Hamilton et al., 1954), or (*b*) if hypertensive crises were observed and recorded. According to these rigorous criteria, hypertension was present in 57 patients and absent in only 1 (*Table V*, *Figs*. 1 and 2). In 10 (17 per cent) it was sustained, in 28 (48 per cent) it was paroxysmal only and in 19 (33 per cent) it was sustained with superadded paroxysms. One patient, while being hypertensive on occasions, also had *hypo*tensive crises (Ramsay and Langlands, 1962). One of the two patients with apparent renal artery stenosis had paroxysmal hypertension only, while the other had sustained hypertension with superadded paroxysms.

The mean blood pressures for the two sexes and the mean relative blood pressures (i.e. in relation to the means of the general population) show considerable hypertension (*Table VI* and *Figs*. 1 and 2), and the females were appreciably more hypertensive than the males. Two patients, a man of 40 and a woman of 43, had suffered cerebrovascular accidents, with hemiplegia, before their phaeochromocytomas were diagnosed.

Hypertensive retinal changes (Keith et al., 1939) were present in 13 patients: grade I in 4, II in 5, III in 2 and IV in 2.

Paroxysms: Most (50) of the patients complained of 'paroxysms' (*Table V*), the main symptoms being palpitations (41), sweating (30), headache (25), anxiety (20), chest pain (16) and abdominal pain (12). One patient was able to induce paroxysms by rubbing his flank. All paroxysms were probably accompanied by hypertensive crises, but these were actually observed in only 47 patients.

Metabolic disturbances: Nine patients had overt diabetes, abnormal glucose tolerance curves or glycosuria. One required treatment with insulin, two with oral hypoglycaemic agents and one with diet alone. The others did not receive any special treatment.

Three patients had hypercalcaemia without any cause, other than phaeochromocytoma, being found (Gray and Gillon, 1976).

Haematuria: Two patients with phaeochromocytomas in the bladder had haematuria. One also had paroxysmal giddiness on micturition.

Pregnancy: Phaeochromocytomas were diagnosed during pregnancy in 4 patients, all of whom had had previous pregnancies complicated by hypertension and/or fetal abnormalities or deaths. In a fifth patient a tumour was seen in the right adrenal at laparoscopy for sterilization shortly after childbirth.

Table I: DISTRIBUTION OF PATIENTS BY CENTRE, SOURCE OF TUMOUR AND SEX

	Source of tumour				
	Operation		Autopsy		
Centre	M	F	M	F	Total
Hammersmith	14	7	2	0	23
Belfast	10	7	5	4	26
Newcastle	8	12	1	2	23
Totals	32	26	8	6	72
Totals	58		14		72

Total males, 40; total females, 32.

Table II: AGES OF PATIENTS AT TIME OF DIAGNOSIS

Age (yr)	In life	At autopsy
0–9	1	0
10–19	3	1
20–29	6	1
30–39	14	3
40–49	19	4
50–59	11	1
60+	4	4
Total	58	14

Table III: DURATION OF SYMPTOMS AT TIME OF DIAGNOSIS

Duration (yr)	In life	At autopsy
<1	20	12
1–2	11	1
2–3	6	1
3–4	9	—
4–5	2	—
5+	10	—
Total	58	14

Table IV: ASSOCIATED MAJOR LESIONS IN 72 PATIENTS

Lesion	No.
Related	
Neurofibromatosis	7*
Medullary carcinoma (MEA II)	3
Renal artery stenosis	2*
Cerebellar haemangioblastoma	1
Total	13
Probably incidental	
Duodenal ulcer	3†
Gallstones	2
Pituitary tumour	1†
Ulcerative colitis	1
Total	7

* One patient had neurofibromatosis and renal artery stenosis.

† One patient had a duodenal ulcer and a pituitary tumour.

Table V: MAIN CLINICAL FEATURES IN 58 PATIENTS DIAGNOSED IN LIFE

	No.	%
Hypertension	57	98
Paroxysms	50	86
Diabetes	9	16
Hypercalcaemia	3	5
Haematuria	2	3
Hemiplegia	2	3

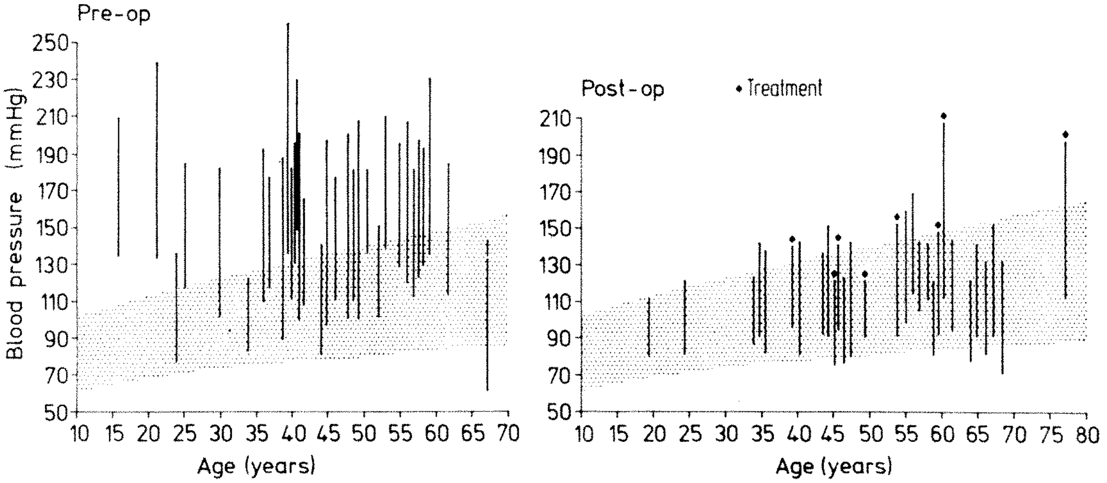

Fig. 1. Blood pressures in male patients before and after operation. The upper and lower borders of the shaded areas depict the mean systolic and diastolic pressures, respectively, of the general population (*see* text). Each vertical line represents one patient and its position indicates his age. Preoperatively, the tops and bottoms of the lines are the means of, respectively, all the systolic and diastolic blood pressure recordings in the 32 patients, excluding those obtained during paroxysms. Postoperatively, they show the *latest* measurements obtained in the 29 patients who survived operation. ◆ indicates that the patient was receiving antihypertensive therapy at the time.

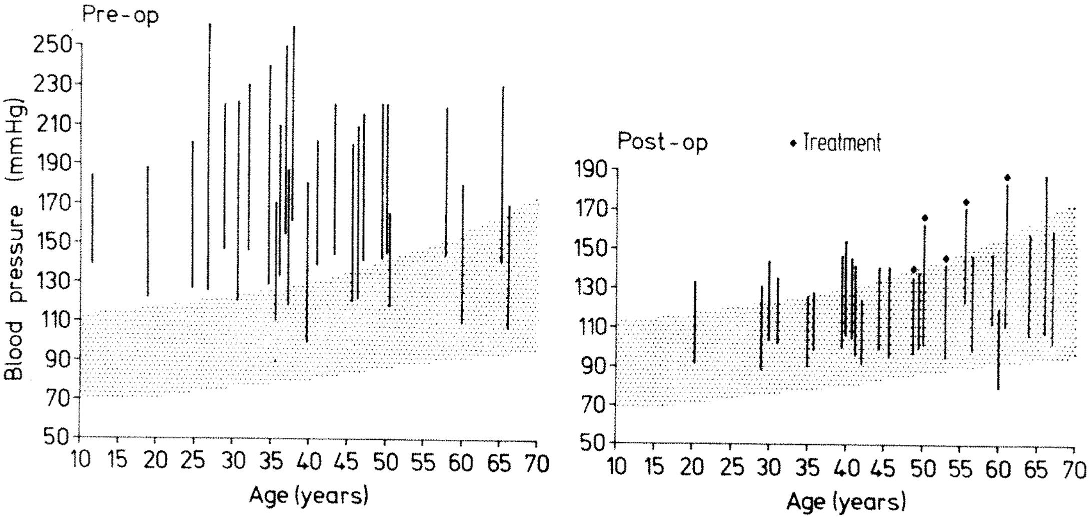

Fig. 2. Blood pressures in female patients before and after operation. The conventions are the same as in *Fig.* 1. Of 26 patients who underwent operation, 25 survived.

Patients diagnosed at autopsy: Phaeochromocytomas had not been suspected during life in 14 patients in whom they were found at autopsy. Retrospective analysis of their case histories suggested that symptoms attributable to their tumours had been present for less than 1 year in 12 (*Table II*). These patients can be divided into three groups according to their modes of death. Those in the first group (9 patients) died from cardiovascular disease, which took the form of myocardial infarct and/or left ventricular failure in 6 (1 of whom died in childbirth), congestive cardiac failure in 1, a cerebrovascular accident in 1 and rupture of an aortic aneurysm in 1. All but the last of these deaths were probably attributable to hypertension and/or catecholamine cardiomyopathy caused by the phaeochromocytoma. The second group (of 3 patients) died from unexpected cardiac arrest associated with relatively minor trauma. One suffered a head injury, 1 underwent vaginal hysterectomy and 1 had an operation for an injury to the eye. All these events presumably precipitated paroxysmal hypertension and acute cardiac dysfunction. Those in the third group (2 patients) died from associated lesions.

One with a cerebellar haemangioblastoma developed neurological signs suggestive of encephalitis, and 1 with a medullary carcinoma of the thyroid, in whom phaeochromocytomas had been sought in life but not found, died from carcinomatosis.

Methods

Diagnosis

The diagnosis of phaeochromocytoma, which was suspected on clinical grounds, involved biochemical tests for the presence of a tumour and, when these were positive, radiological and other investigations to determine its site.

Presence of tumours: The diagnostic biochemical tests included measurement of vanylmandelic acid (VMA), metadrenalines

Table VI: MEAN BLOOD PRESSURES AND RELATIVE BLOOD PRESSURES* BEFORE OPERATION AND AT LATEST OBSERVATION AFTER OPERATION (see text)

	Sex/no.		Absolute	Relative
Preop.†	M/32	Syst.	180·2±32·4 (1)	+59·0±29·0 (3)
		Diast.	106·3±20·9 (2)	+29·0±17·3 (4)
	F/26	Syst.	213·0±31·2 (1)	+73·1±26·1 (3)
		Diast.	133·6±16·8 (2)	+45·8±17·7 (4)
Postop.‡	M/29	Syst.	134·4±22·7	+6·4±8·7
		Diast.	80·4±17·6	+5·3±4·7
	F/25	Syst.	132·7±15·7	+6·5±6·8
		Diast.	89·0+6·4	+8·8+5·4

All values are mmHg, mean±1 s.d.

Syst., systolic; Diast., diastolic.

* I.e. patient's mean blood pressure minus that of the mean for members of the general population of the same age and sex.

† Statistical comparisons of males and females preoperatively:

	t (56 d.f.)	P
(1) Absolute systolic	3·90	<0·001
(2) Absolute diastolic	5·39	<0·001
(3) Relative systolic	1·92	<0·1
(4) Relative diastolic	3·64	<0·001

‡ Postoperatively 8 males and 5 females were receiving antihypertensive therapy when their blood pressures were measured.

(MAs) and catecholamines (CAs) in the urine and often, in the later years, measurement of CAs in the blood. In some patients adrenaline and noradrenaline were measured separately. The tests were usually done several times. VMA was measured in all 58 patients and was elevated in 57 (*Fig.* 3). MAs were measured in 16 and were high in 15 and urinary CA was measured in 37, being high in 34. All patients whose excretion of one was normal had high levels of one or both of the others. Catecholamine levels in the blood have been reported elsewhere (Jones et al., 1977).

Pharmacological tests (particularly with histamine and phentolamine) were used also in many of the earlier patients, but were abandoned because of their unreliability and potential danger.

Localization of tumours: Attempts to locate the tumours were made radiographically, and occasionally by other methods, in 53 of the 58 patients undergoing operation. Four tumours were palpable and, as already mentioned, the side on which the tumour was located was established by the patient's observation of the effect of massage.

The radiologists did not all use the same methods. At first, in Hammersmith and Newcastle, intravenous urography (IVU), presacral insufflation and selective arteriography were used, in that order, until the tumour had been located. Later, selective venous sampling was added to the list of investigations. In Belfast the same course was followed, but insufflation was not used. In the later years all three centres preferred IVU with nephrotomography, followed by arteriography and selective venous sampling, and insufflation was used rarely. Several years ago the form of preparation and control of blood pressure employed for surgical operations was introduced for invasive radiological procedures (*see below*).

Tumours were located accurately in 47 patients (81 per cent) (*Fig.* 3). Two bladder tumours were suspected on arteriography and cystoscopy. One was clearly visible through the cystoscope and the other was seen as an abnormality, though not clearly neoplastic, in the roof of the bladder. Localization was unsuccessful preoperatively in 4 patients, but none of them had caval catheterization. In 5 patients no attempt at localization was made, owing to pregnancy in 3 and because the operations were undertaken as emergencies in 2.

Sites of tumours: Seventy-eight tumours were identified in the 72 patients, and their sites, determined at operation or at autopsy, are shown in *Fig.* 4. All were within the abdomen. In 59 patients (82 per cent) the tumours were in the adrenals, with only a slight preponderance on the right side. In 6 of these the tumours were bilateral. Two of the 6 had Sipple's syndrome (MEA II) and another had several tumours in one gland (counted as one in the total). In 13 patients (18 per cent) the tumours were at extra-adrenal sites, 8 close to the kidneys, 2 in the organ of Zuckerkandl, 2 in the bladder and 1 adjacent to the inferior vena cava above the adrenal.

Sizes of tumours: All the tumours were spherical or ovoid in shape and 63 (81 per cent) measured between 2 and 10 cm in their greatest diameters (*Table VII*). The largest tumour measured 20 cm.

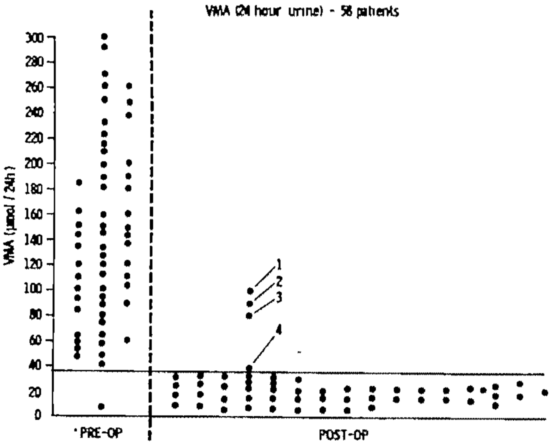

Fig. 3. Urinary vanylmandelic acid excretion before and after operation. Each point represents the means of all readings in one patient. All 58 patients are included before operation. The 54 points after operation represent the latest measurements in those who survived. In all but 3, 2 of whom died and 1 of whom was lost to follow-up within 1 year, the measurements were made from 1 to 20 years after operation. The upper limit of normal is 37 µmol/24 h. Key: 1 and 2 had malignant lesions incompletely removed; 3 had benign locally recurrent disease; 4 possibly had a second tumour.

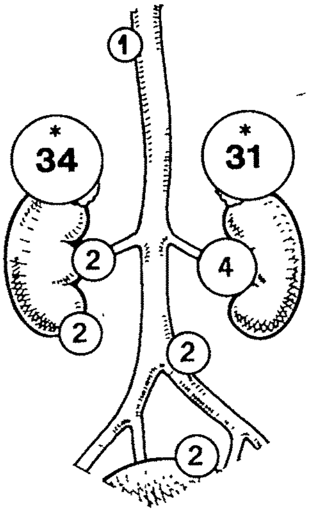

Fig. 4. Sites of 78 tumours in 72 patients.* Bilateral in 6.

Treatment

All patients in whom phaeochromocytomas were diagnosed during life were submitted to surgical operation.

Control of blood pressure: Initially the need for pharmacological preparation for operation was not generally appreciated, and it

Table VII: SIZES OF PHAEOCHROMOCYTOMAS IN 72 PATIENTS

Diameter (cm)	No. of tumours
0–<2	8
2–<5	37
5–<10	26
10+	7
Total	78

Table VIII: INFLUENCE OF METHOD OF MANAGEMENT ON OPERATIVE MORTALITY

Method of management	Patients	Operations	Deaths
Old regimen	17	17	3 (18%)
New regimen	41	45	1 (2%)

Statistical comparison:
3/17 *v.* 1/41: exact $P = 0{\cdot}07$.
3/17 *v.* 1/45: exact $P = 0{\cdot}06$.

Table IX: HISTOPATHOLOGY OF TUMOURS AND RECURRENCE

	No. of patients	
	Benign	Malignant
Found at autopsy	14	0
Diagnosed in life	53	5
Recurred	2 (4%)	2 (40%)

was not employed. Blood was replaced quantitatively, phentolamine was injected when the blood pressure rose excessively, especially during handling of the tumour, and noradrenaline or metaraminol was infused after removal of the tumour when, as was usually the case, hypotension ensued.

During 1967 a new regimen was introduced, which involved preoperative preparation with an alpha-adrenergic blocking agent, the appropriate use of beta-blockers and infusion to increase the blood volume after removal of the tumour (Ross et al., 1967). After this only 1 patient was treated by the old regimen.

Preoperatively, in Hammersmith and Newcastle, the alpha-blocker phenoxybenzamine was used most commonly and, in Belfast, guanethidine, chlorpromazine or phenoxybenzamine, either alone or in combination, was employed (Bingham et al., 1972). In all centres beta blockade (usually propranolol) was given only in the event of tachycardia or cardiac irregularity (Montgomery and Welbourn, 1975). It was required commonly during operation, but rarely before. Phentolamine and phenoxybenzamine, alone or in combination, were given intravenously in the event of severe hypertension during operation. In addition to the quantitative replacement of blood, additional blood, plasma or dextran was infused rapidly after removal of the tumour and then more slowly until the blood pressure was stable. The volume to be infused was assessed by continuous monitoring, during and after operation, of arterial and central venous pressures. The arterial pressure proved to be the more helpful, since reliance on the latter led to overtransfusion on occasions. The need for beta blockade was assessed by continuous monitoring of the heart rate and the ECG during and after operation.

Formerly the operations were fraught with hazards and with anxiety for the surgeon, anaesthetist and all concerned. After experience of the careful use of effective pharmacological control and blood volume replacement, operations for the removal of phaeochromocytomas became much less hazardous. However, as with any operation, there were sometimes serious complications. One patient, for instance, required an emergency gastrectomy for a bleeding duodenal ulcer 2 days after removal of bilateral tumours. He had papilloedema and retinal haemorrhages before the first operation and lost his sight after the second.

Operations: The abdomen was explored widely and tumours were removed through anterior abdominal incisions, usually midline or transverse epigastric, unless there were special reasons for other approaches (Welbourn, 1977). For instance, lateral thoracoabdominal incisions were used for large tumours, especially on the right, and for patients who had had previous upper abdominal operations on the adrenals or other viscera. Lower incisions were used for tumours sited below the kidneys or in the bladder. Renal biopsies were taken in some patients for evaluation of the effects of hypertension on the kidneys. On five occasions, for various reasons, it was necessary to remove a kidney with a phaeochromocytoma.

Sixty-two operations were undertaken in the 58 patients, second operations being needed in 4. One of these had a previously unsuspected second tumour removed 2 weeks after the first. Two had local recurrences of benign tumours (*see below*). A fourth patient was suspected of having a second tumour, but none could be found on re-exploration.

Operative mortality: The introduction of the new regimen not only transformed the conduct of the operation, but was followed by a reduction in the operative mortality from 18 per cent to 2 per cent (*Table VIII*).

With the old regimen 3 patients died at operation or in the immediate postoperative period. One succumbed from cardiac arrest while being explored in an uncontrolled hypertensive crisis (Cowley et al., 1970), a second suffered a cerebrovascular accident during induction of anaesthesia and the third patient developed cardiac dysrhythmia during operation, remained in cardiac failure and died 3 days later from pulmonary emboli.

Between 1968 and 1976 41 patients were treated surgically with 1 operative death, which was probably due to the overuse of beta blockade.

Pregnancy: All 4 patients whose phaeochromocytomas were diagnosed in pregnancy survived removal of their tumours, but only 2 produced healthy babies. One, in whom the diagnosis was made at 3 months, had her pregnancy terminated by Caesarean section and the tumour removed at the same operation. A second patient, diagnosed at 5 months, was maintained on alpha- and beta-blockers until term, when a healthy baby was born. Treatment was continued and the tumour was removed 2 months later. The third case, diagnosed at 7 months, was treated with phenoxybenzamine, but the fetus died *in utero*. Shortly afterwards, the fetus was removed by Caesarean section and the tumour was excised at the same operation. The fourth patient was not diagnosed until 8 months, but was treated with phenoxybenzamine, underwent premature labour and had a healthy baby. The tumour was removed soon after.

Bilateral tumours: Four patients underwent bilateral adrenalectomy. Three required permanent replacement therapy, but in one sufficient cortical tissue was left for steroids to be withdrawn after a few months. The other 2 patients with bilateral tumours were diagnosed post mortem.

Histopathology and recurrence

Tumours were reported as malignant in 5 patients (*Table IX*), all of whom were diagnosed in life. Three, who had been treated by surgical excision (together with nephrectomy and radiotherapy in 1 case), showed no sign of recurrence after 8, 8 and 9 years, respectively. The fourth, who was first seen with massive local recurrence and invasion of adjacent tissues after operation elsewhere, was treated by partial surgical removal and radiotherapy. One year later he was alive and in fair health, but had clinical and biochemical evidence of recurrence. The fifth had a large tumour adherent to the kidney, necessitating nephrectomy in addition to adrenalectomy. This patient developed widespread metastases, was treated by radiotherapy and cyclophosphamide, but died after 6 months.

Two of the tumours reported as benign recurred locally. One (Sellwood et al., 1970) had had a tumour removed elsewhere 11 years previously (probably with rupture and spillage) and had developed multiple recurrent lesions in the tumour bed, many of which were excised. Ten years later further extensive recurrences had developed retroperitoneally, extending into the head of the pancreas and the lesser sac. They were treated by partial removal and fast neutron therapy, without benefit,

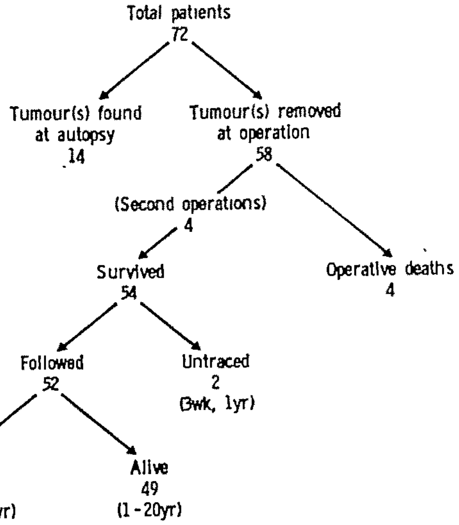

Fig. 5. Overall analysis of outcome in 72 patients.

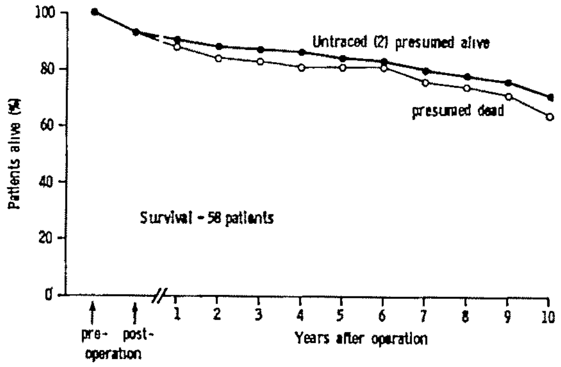

Fig. 6. Survival of 58 treated patients, as percentages, to 10 years after operation. For details *see* text.

but the patient was alive and relatively well 1 year later. The other patient had a benign tumour in the organ of Zuckerandl which was excised incompletely. Multiple local recurrences developed 3 years later and were removed. The patient remained well 6 years later.

Long term results

Survival

Of the 72 patients (*Fig.* 5), phaeochromocytomas were diagnosed at autopsy in 14 and removed by operation in 58. Of the latter, 4 died in the immediate postoperative period and 54 survived (4 of them having undergone second operations without mortality). Two of the 54 were untraced (after 3 weeks and 1 year, respectively) and 52 were followed either to date (1976 or 1977) or until death. Three of these died (after 2 months, 6 months and 9 years, respectively) and 49 were alive at between 1 and 21 years after operation.

The 2 patients who could not be traced in 1976 and 1977 had been well 3 weeks and 1 year after operation and had then emigrated. Two of the 3 late postoperative deaths resulted from the effects of the phaeochromocytoma or of attempts to treat it. One patient, who had had a phaeochromocytoma in the bladder, died after 3 months from pulmonary embolus complicating an operation for intestinal obstruction, caused by a loop of small intestine adhering to the scar on the roof of the bladder. The second, a male of 44, who has been described already, died from widespread metastatic disease 6 months after operation. A third patient, a man aged 48 at the time of operation, died from a myocardial infarct 9 years later.

Table X: NUMBERS OF PATIENTS ALIVE AND DEAD FROM TIME OF INITIAL TREATMENT

Years after treatment	No. treated	No. dead		No. alive*	% alive, assuming untraced patients to be	
		Immediately after op.	Later		Alive	Dead
1	58	4	2	51 (1)	90	88
2	50	4	2	42 (2)	88	84
3	48	4	2	40 (2)	87	83
4	42	4	2	34 (2)	86	81
5	37	4	2	30 (1)	84	81
6	36	4	2	29 (1)	83	81
7	25	4	1	19 (1)	80	76
8	23	4	1	17 (1)	78	74
9	17	3	1	12 (1)	76	71
10	14	3	1	9 (1)	71	64
11	11	2	0	8 (1)	82	73
12	10	2	0	7 (1)	80	70
13	10	2	0	7 (1)	80	70
14	7	2	0	5 (0)	71	71
15	4	1	0	3 (0)	75	75
16	4	1	0	3 (0)	75	75
17	3	0	0	3 (0)	100	100
18	3	0	0	3 (0)	100	100
19	2	0	0	2 (0)	100	100
20	1	0	0	1 (0)	100	100

* Numbers in parentheses, patients untraced.

The survival data (*Table X, Fig.* 6) have been calculated in two ways—on the assumption that both the untraced patients were alive at the time of the final review and on the assumption that both died as soon as they were lost. The two lines on the graph in *Fig.* 6 are very close and show a gradual fall in the number of patients surviving up to 10 years after operation. At this time between 64 and 71 per cent of the series were alive. Thereafter the total number of patients becomes very small, but it is clear that the long term prognosis is excellent.

No separate analyses are shown either for patients with benign or malignant lesions, because their survival was similar, or for those treated by the two regimens, because these affected only the operative mortality.

The 2 patients with multiple endocrine adenopathy diagnosed in life both had medullary carcinomas that could not be eradicated. One, a man of 24, whose thyroid tumour had invaded the recurrent laryngeal nerve and the larynx, was treated by local excision and radiotherapy and he was well 1 year later. The other, a woman of 50, was found to have hepatic medullary metastases when a right-sided phaeochromocytoma was removed. There was no obvious goitre, but the patient developed myxoedema, was treated with thyroxine and remained well 7 years later. She had no evidence of a phaeochromocytoma in the remaining adrenal.

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Blood pressure
Paroxysms of hypertension were relieved by operation in all who had suffered them previously. The mean blood pressures fell appreciably, but sustained hypertension (as defined earlier) persisted in many patients (*Table VI*; *Figs*. 1 and 2). In fact only 6 patients (5 of them male) were normotensive without specific therapy. Eight males and 5 females were receiving antihypertensive therapy, but only 1 (a male) had achieved a normal pressure. The hypertension (at least with specific therapy) caused little disability and no longer threatened life. It was sometimes difficult to discover whether persistent hypertension was due to residual or recurrent tumours or to circulatory or renal damage. Renal biopsy at the time of operation was helpful in a few cases. The neurological state of those who had had strokes before operation remained unchanged.

It has been mentioned that 2 patients had radiological appearances of renal artery stenosis. One, a woman of 39 with paroxysmal hypertension, had a malignant tumour in the left adrenal almost surrounding the renal pedicle. Damage to the renal vein at operation necessitated nephrectomy, but the renal artery showed no histological abnormality. Nine years later the patient had mild sustained hypertension. The other, a woman of 60, with sustained and paroxysmal hypertension, had a left-sided adrenal tumour. No abnormality was found in the renal artery at operation. Three weeks later the blood pressure was 120/80 mmHg, but the patient has not been traced since.

Metabolic disturbances
Of the 9 patients with diabetes, 2 died postoperatively, 4 were cured, 1 still required insulin and 2, 1 of whom had malignant disease, continued to require oral hypoglycaemic drugs.

Hypercalcemia was abolished by removal of phaeochromocytomas in 2 patients, but persisted after the removal of two tumours in a further patient. No cause could be found.

Urinary catecholamines and metabolites
Urinary VMA levels fell to normal after operation in all but 4 patients (*Fig*. 3). Of these, 2 had malignant disease, 1 had locally recurrent benign disease and 1, whose level was only just above normal, is being investigated for recurrence. Urinary MAs were not measured in any patients after operation. Urinary CAs were measured in 21 and were normal in all; they were not measured in the 1 patient whose VMA was slightly raised and who was suspected of having a second tumour.

Discussion

This study reveals that, when the diagnosis of phaeochromocytoma is suspected, localization can be achieved safely and accurately in the great majority of cases and that removal can be accomplished safely, provided that alpha- and beta-blockers are used carefully. Many patients, however, still die before the diagnosis is made.

Autopsy cases
Fourteen, or 19 per cent, of the patients were diagnosed for the first time at autopsy. Others have made similar observations. Graham (1951), in an early collective review, referred to 72 of 207 patients (35 per cent) who died without operation, but it is not clear how many of these had not been diagnosed in life. Scott and his colleagues (1976), with modern diagnostic methods available, found tumours at autopsy in 11 of 44 patients (25 per cent). In the present series different proportions were found at autopsy in the three centres. The highest (35 per cent) was found in Belfast, where two laboratories handle all the pathological material (biopsy and autopsy) from the Province of Northern Ireland, which is a fairly stable community of about 1·5 millions with few patients referred from abroad. The lowest proportion (9 per cent) was in Hammersmith, which accepts many patients, particularly with such rare lesions, already diagnosed or suspected in life, from all over Britain and from abroad. The intermediate position of Newcastle (13 per cent) probably reflects the fact that patients were referred for operation from the whole of northern England, while pathological material was obtained from only two laboratories in Newcastle. The true proportion of patients with phaeochromocytomas which are not diagnosed in life is, therefore, probably at least 35 per cent.

If these patients were diagnosed in life, most of them could be treated effectively. A high index of suspicion and appropriate investigation should bring more cases to light. The pointers are (*a*) hypertension, especially if paroxysmal or in pregnancy; (*b*) paroxysms of any sort, particularly if accompanied by palpitations, sweating, headache, anxiety or pain in the chest or abdomen; (*c*) neurofibromatosis; and (*d*) medullary carcinoma of the thyroid. Appropriate screening tests (urinary VMA, MAs or CAs) applied to these patients should increase the number diagnosed in life.

Chemical diagnosis and localization
There is considerable disagreement in the literature about the best chemical tests for the diagnosis of phaeochromocytoma (ReMine et al., 1974; Harrison et al., 1975). The data show that, in this series, measurement of urinary VMA was more accurate than many other workers have found it. When clinical suspicion continued, despite normal VMA values, other tests were negative in all but one patient (*Fig*. 3). We now regard the measurement of CAs in the urine and/or blood as the most reliable diagnostic method.

False high VMA readings are caused by various factors, including stress and drugs (Montgomery and Welbourn, 1975). With care these factors should be excluded, but we have not always succeeded in doing so.

In this series the location of the tumours was established accurately before operation in 81 per cent of patients and in 89 per cent of those in whom it was attempted. These figures are better than any published previously. Although nephrotomography, selective arteriography and selective venous sampling were the best methods, CAT scanning, ultrasonography and adrenal scintigraphy (Thrall et al., 1978) may play a major role in the future. False positive findings have been reported (Öhman et al., 1974) and, although we did not encounter any in this series, we have done so since.

False positive chemical diagnoses and/or localization studies have caused us to operate, without finding tumours, on 5 patients in the past few years (during the period of this study and since), so that we still have much to learn. However, it is probably better to operate unnecessarily than to fail to operate on a patient who has a phaeochromocytoma.

Location

In this series 13 of 72 patients (8 per cent) had tumours outside the adrenals. This is about the average for all published series, the extremes being zero (Sander et al., 1971—0/20) and 17 per cent (Melicow, 1977—17/100). Tumours outside the abdomen are exceptionally rare. There were none in this series and 2 (2 per cent) in Melicow's.

Bilateral tumours and multiple endocrine adenopathy, type II

In Graham's (1951) review, 19 of 207 cases (9 per cent) had bilateral tumours. The association with medullary carcinoma had not then been described and the number who had both lesions is not known. It is now clear that many of those with bilateral lesions have thyroid tumours also, but the exact number in each series is not always stated. In most recent reports the proportions of patients with bilateral adrenal tumours have been lower than in Graham's series (this series, 6/72—8 per cent; Öhman et al., 1974, 0/20—0 per cent; ReMine et al., 1974, 6/138—4 per cent; Scott et al., 1976, 3/44—7 per cent; Melicow, 1977, 3/100—3 per cent). The only exception is the series of Sander et al. (1971), who found bilateral tumours in 6 of 21 patients (29 per cent), 2 of whom developed second tumours later (38 per cent). Patients with more than two phaeochromocytomas and with multiple tumours in extra-adrenal sites appear to be very rare indeed. However, we have recently treated a patient who had one tumour in the bladder, two others close to it and none in the adrenals.

The proportion of patients with medullary carcinoma (MEA II) (3/72) was similar to that found by Scott et al. (1976) (2/44) and by ReMine et al. (1974) (4/138). However, the numbers of such patients reported in future series are likely to be greater, now that the syndrome is well recognized. It is important to search for phaeochromocytomas in patients with medullary carcinoma, and to treat them first, to avoid sudden death during investigation or treatment of the thyroid lesions (Beaugie et al., 1975). Phaeochromocytomas are so often bilateral (eventually, if not initially) in this syndrome (as in 2 of the 3 patients in this series), that, even if only one is found, bilateral total adrenalectomy is probably the procedure of choice (Carney et al., 1976). It is probably unwise to attempt to leave cortical tissue, in the hope of avoiding the need for replacement therapy. Local recurrence of tumour, sometimes malignant, has been reported in some patients subjected to this procedure (Bloom and Fonkalsrud, 1974; Carney et al., 1976).

Operative mortality

The introduction of the new regimen (preparation with alpha blockade and restoration of blood volume) undoubtedly reduced the hazards of operation, but the apparent reduction of operative mortality (from 18 per cent to 2 per cent) is not statistically significant (*Table VIII*). It is probably real, but information from other reports and from personal inquiries do not allow a valid comparison to be made. For instance, in the series of ReMine et al. (1974) 4 of the 138 patients died (3 per cent), all before the introduction of the new regimen. However, the numbers of patients in each group are not stated and, since 1926, when the first patient was treated, many other significant advances in anaesthesia and general care have been introduced.

Malignancy

It is very difficult, on histological grounds, to determine whether a phaeochromocytoma is benign or malignant, and the same criteria may not have been used in all series. The reported incidence varies from nil (Sanders et al., 1971) to 13 per cent (ReMine et al., 1974) and the pooled data from seven major series, including these two and the present one, is 10 per cent (60/602) (Graham, 1951; Öhman et al., 1974; Scott et al., 1976; Melicow, 1977). It is surprising how well many of those with malignant tumours fare after operation.

Blood pressure

The analysis of blood pressure, and of the effect of operation, in this series is more detailed than in any published previously. The significantly greater degree of hypertension in women than in men before operation is a new observation for which there is no obvious explanation. ReMine et al. (1974) report that 27 per cent of patients (28/103) had persisting hypertension 1 year after operation while the remainder had normal pressures. These authors do not define hypertension. Harrison et al. (1975) state that, even if the pressure remains high for a time after operation, it tends to fall eventually. The present data do not support this view.

Metabolic disturbances

Diabetes is well known in patients with phaeochromocytomas (Manger and Gifford, 1977) and was present in 16 per cent of the patients whom we diagnosed in life. It may be due to catecholamine (particularly adrenaline) excess and be cured by removal of the tumours, as in 4 of our patients. If the diabetes is not relieved by complete removal of the tumours, as in 2 of these cases, it is probably an associated but unrelated, disease. It is worth noting that 2 of the 9 patients (22 per cent) died postoperatively.

The significance of hypercalcaemia in association with phaeochromocytoma is unknown and our observation that removal of the tumour corrected it in 2 of 3 patients agrees with previous reports (Swinton et al., 1972).

Survival

The survival data in this series are more complete than in any previously reported. ReMine et al. (1974) operated on 138 patients, 134 of whom survived. They state that 6 (4 per cent) were lost to follow-up from 1 to 10 years after operation, but conclude that the actuarial survival curve for patients with benign lesions was similar to that for the 'normal' population. They apparently make no allowance for the possible deaths of those who were not traced. In their series patients with malignant tumours fared much worse than those with benign ones. In this series there were only 5 patients with malignant tumours and, of them, only 1 died during the follow-up period. Patients came from so many different countries that the calculation of actuarial survival curves was not appropriate.

Survival data from other reported series are too few for valid comparison.

Pregnancy

In our series 4 tumours were diagnosed during pregnancy. All the mothers survived, but 2 fetuses perished. Of the 2 patients discovered later to have phaeochromocytomas, 1 died during delivery, but both babies survived. This experience is similar to that of others. A review of the literature (Schenker and Chowers, 1971) shows that 58 per cent of mothers and 56 per cent of fetuses die when the condition is not diagnosed.

If the diagnosis is made during pregnancy, the outlook is better for the mother (17 per cent mortality) but the fetal mortality remains high. A phaeochromocytoma should be suspected in any pregnant woman with hypertension or sweating. If a tumour is diagnosed in the first two trimesters, immediate removal under adrenergic blockade is probably advisable, despite the high risk of abortion. Localization by ultrasound (though not by radiography) is safe. The value of long term medical management as an alternative to operation has not been evaluated thoroughly, but there is no evidence that it reduces the fetal mortality.

In the third trimester adrenergic blockade to control the hypertension and to allow the fetus to reach maturity is probably advisable. Delivery by Caesarean section and simultaneous removal of the tumour, if feasible, may then be undertaken at the appropriate time. If the tumour has not been localized, and if it cannot be found easily at operation, alpha blockade may be continued, further localization studies undertaken and the tumour removed later (Montgomery and Harley, 1977).

Recurrence

In one of our patients paroxysms returned some years later and were found to be due to recurrent benign phaeochromocytoma.. This represented benign implantation and growth of phaeochromocytoma tissue spilt during tumour removal and emphasizes the need to ensure total removal of the lesion (Sellwood et al., 1970; Sivula, 1974).

Duodenal ulcer

Three patients (4 per cent) had duodenal ulcers, an incidence no greater than that in the general population. One ulcer, however, was particularly severe, and it seems possible that stimulation of gastrin release by catecholamines may have played a part (Hayes et al., 1972). If so, it is surprising that similar incidents are not encountered more frequently.

Conclusion

The main lessons to be learned from this study are that (*a*) many phaeochromocytomas remain undiagnosed until after death; (*b*) appropriate investigation of suspect patients would probably bring more tumours to light; (*c*) some 90 per cent of tumours are benign; (*d*) appropriate preparation and surgical removal carry a very low operative mortality; (*e*) although hypertension may persist in many, it is susceptible to medical therapy and no longer constitutes a threat to life; and (*f*) the long term prognosis is excellent.

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References

BEAUGIE J. M., BELCHETZ P. E., BROWN C. C. et al. (1975) Report of a family with inherited medullary carcinoma of the thyroid and phaeochromocytoma. *Br. J. Surg.* 62, 264–268.

BEER E., KING F. H. and PRINZMETAL M. (1937) Pheochromocytoma with demonstration of pressor (adrenalin) substance in blood preoperatively during hypertensive crisis. *Ann. Surg.* 106, 85–91.

BINGHAM W., ELLIOTT J. and LYONS S. M. (1972) Management of anaesthesia for phaeochromocytoma. *Anesthesia* 27, 49–60.

BLOOM D. A. and FONKALSRUD E. W. (1974) Surgical management of pheochromocytoma in children. *J. Pediatr. Surg.* 9, 179–184.

CARNEY J. A., GLEN P. D., SIZEMORE G. W. et al. (1976) The pathology of the adrenal medulla in multiple endocrine neoplasia type 2—phaeochromocytoma and its precursors. *Am. J. Clin. Pathol.* 66, 280–290.

CHAPMAN R. C. and DIAZ-PEREZ R. (1962) Pheochromocytoma associated with cerebellar hemangioblastoma. *JAMA* 182, 1014–1017.

COWLEY D. J., MONTGOMERY D.A.D. and and WELBOURN R. B. (1970) Management of paroxysms of hypertension in patients with phaeochromocytomas. *Br. J. Surg.* 57, 832–834.

FISCHER I. A., BLUM J. W. and BISWANGERM U. (1973) Epinephrine and the regulation of parathyroid hormone (PTH) and calcitonin (CT) secretions *in vivo*. *Clin. Res.* 21, 623.

FRÄNKEL F. (1886) Ein Fall von doppelseitigem, vollig latent verlaufenen Nebennierentumor und gleichzeitiger Nephritis mit Veranderungen am Circulationsapparat und Retinitis. *Virchows Arch. Pathol. Anat. Physiol.* 103, 244–263.

GLUSHIEN A. S., MARSUY M. M. and LITTMAN D. S. (1953) Phaeochromocytoma: its relationship to the neurocutaneous syndromes. *Am. J. Med.* 14, 318–327.

GRAHAM J. B. (1951) Pheochromocytoma and hypertension. An analysis of 207 cases. *Int. Abstr. Surg.* 92, 105–121.

GRAY R. S. and GILLON J. (1976) Normotensive phaeochromocytoma with hypercalcaemia: correction after adrenalectomy. *Br. Med. J.* 1, 378.

HAMILTON M., PICKERING G. W., ROBERTS J. A. F. et al. (1954) The aetiology of essential hypertension. 1. The arterial pressure in the general population. *Clin. Sci.* 13, 11–35.

HARRISON T. S., GANN D. S., EDIS A. J. et al. (1975) The adrenal medulla. In: *Surgical Disorders of the Adrenal Gland—Physiologic Background and Treatment*. New York, Grune & Stratton, pp. 63–123.

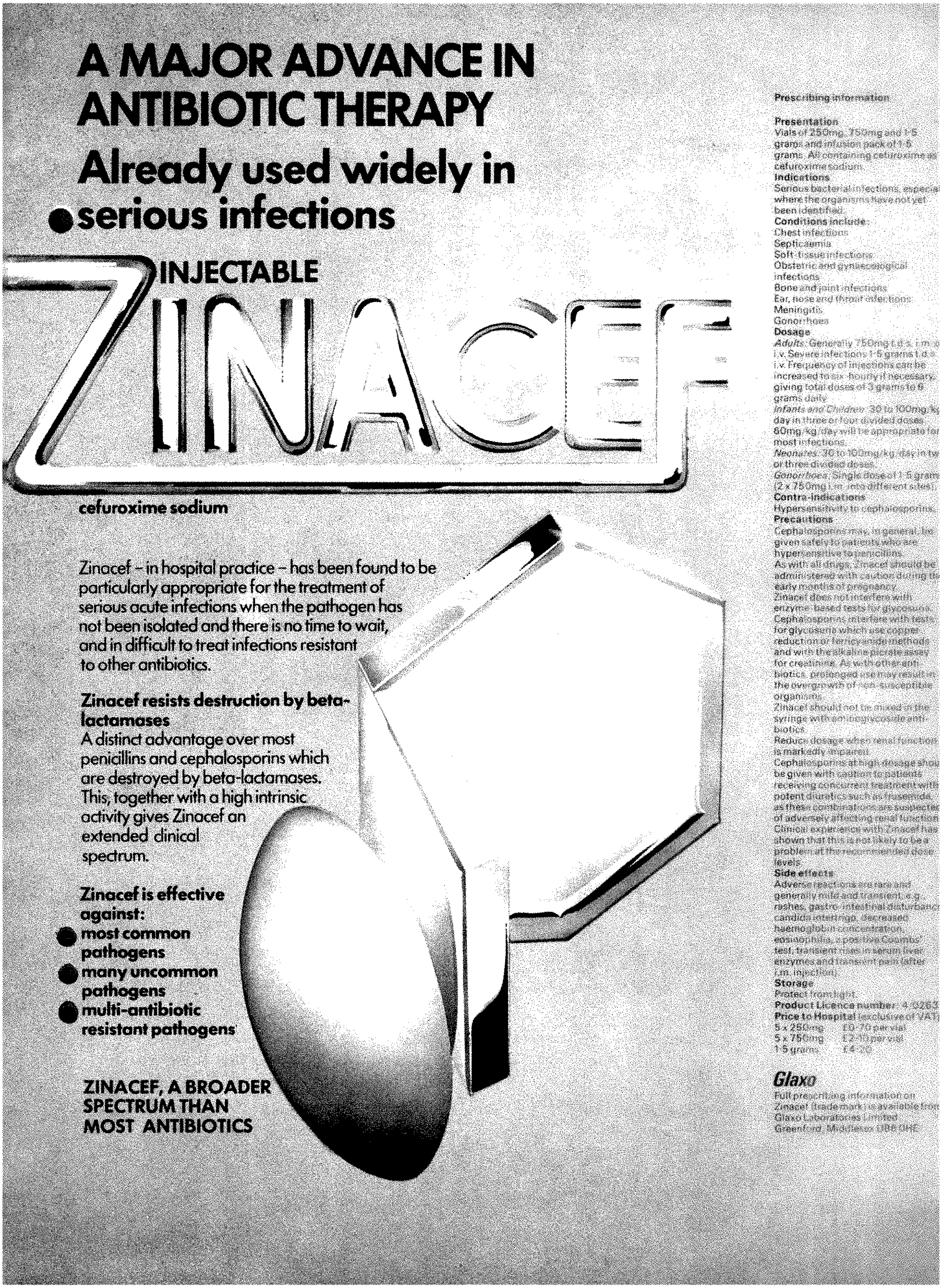
HARRISON T. S. and THOMPSON N. W. (1975) Multiple endocrine adenomatosis I and II. *Curr. Probl. Surg.* (*Chicago*) August, pp. 1–51.

HAYES J. R., KENNEDY T. L., ARDILL J. et al. (1972) Stimulation of gastrin release by catecholamines. *Lancet* 1, 819–821.

HOLTON P. (1949) Noradrenaline in tumors of the adrenal medulla. *J. Physiol.* (*Lond.*) 108, 525–529.

JONES D. H., REID J. L., HAMILTON C. A. et al. (1977) Plasma noradrenaline and selective venous sampling in the diagnosis of phaeochromocytoma. *Clin. Sci. Mol. Med.* 52, 20P.

KEITH N. M., WAGNER H. P. and BARKER N. W. (1939) Some different types of essential hypertension: their course and prognosis. *Am. J. Med. Sci.* 197, 332–343.



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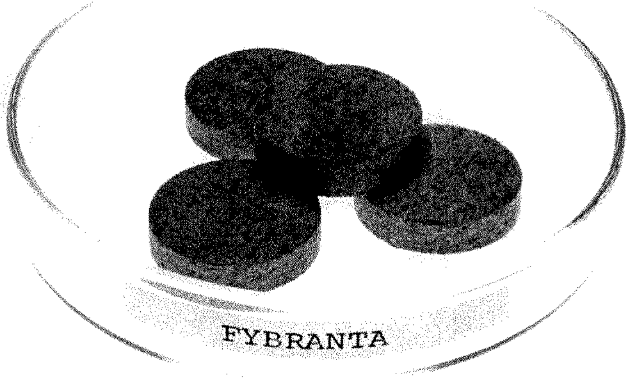

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L'ABBÉ M., TINEL J. and DOUMER A. (1922) Crises solaires et hypertension paroxystique en rapport avec une tumeur surrénale. *Bull. Mém. Soc. Méd. Hôp. Paris* **46**, 982–990.

LAUBRY C. (1927) Hypertension paroxystique guérie par la radiothérapie de la region surrénale. *Bull. Mém. Soc. Méd. Hôp. Paris* **51**, 1216–1218.

MANGER W. M. and GIFFORD R. W. (1977) *Pheochromocytoma*. Berlin, Springer-Verlag.

MAYO C. H. (1927) Paroxysmal hypertension with tumor of retroperitoneal nerve. *JAMA* **89**, 1047–1050.

MELICOW M. M. (1977) One hundred cases of pheochromocytoma (107 tumors) at the Columbia-Presbyterian Medical Centre, 1926–1976. A clinicopathological analysis. *Cancer* **40**, 1987–2004.

MONTGOMERY D. A. D. and HARLEY J. M. G. (1977) Endocrine disorders. *Clin. Obstet. Gynecol.* **4**, 339–370.

MONTGOMERY D. A. D. and WELBOURN R. B. (1975) Adrenal medulla and adrenalectomy. In: *Clinical Endocrinology for Physicians and Surgeons*. London, Arnold, pp. 143–161.

ÖHMAN U., GRANBERG P.-O., HJERN B. et al. (1974) Pheochromocytoma. Diagnosis, management and follow-up in twenty patients. *Acta Chir. Scand.* **140**, 660–666.

PICK L. (1912) Das Ganglioma embryonale sympathicum (Sympathoma embryonale), eine typische bösartige Geschwuestform des sympathischen Nervensystems. *Klin. Wochenschr.* **19**, 16–26.

PINCOFFS M. C. (1929) A case of paroxysmal hypertension associated with suprarenal tumor. *Trans. Assoc. Am. Physicians* **44**, 295–299.

RAMSAY I. D. and LANGLANDS J. H. M. (1962) Phaeochromocytoma with hypotension and polycythaemia. *Lancet* **2**, 126–128.

REMINE W. H., CHONG G. C., VAN HEERDEN J. A. et al. (1974) Current management of pheochromocytoma. *Ann. Surg.* **179**, 740–748.

ROSS E. J., PRICHARD B. N. C., KAUFMAN L. et al. (1967) Preoperative and operative management of patients with phaeochromocytoma. *Br. Med. J.* **1**, 191–198.

SANDER S., MURI O. and MATHISEN W. (1971) Pheochromocytoma: a follow-up study of twenty-one patients. *Acta Chir. Scand.* **137**, 470–473.

SCHENKER J. G. and CHOWERS I. (1971) Pheochromocytoma and pregnancy: review of eighty-nine cases. *Obstet. Gynecol. Surv.* **26**, 739–747.

SCOTT H. W., OATES J. A., NIES A. S. et al. (1976) Pheochromocytoma: present diagnosis and management. *Ann. Surg.* **183**, 587–593.

SELLWOOD R. A., WAPNICK S., BRECKENRIDGE A. et al. (1970) Recurrent phaeochromocytoma. *Br. J. Surg.* **57**, 309–312.

SIVULA A. (1974) Recurrence of benign phaeochromocytoma by intraoperative implantation. *Acta Chir. Scand.* **140**, 334–339.

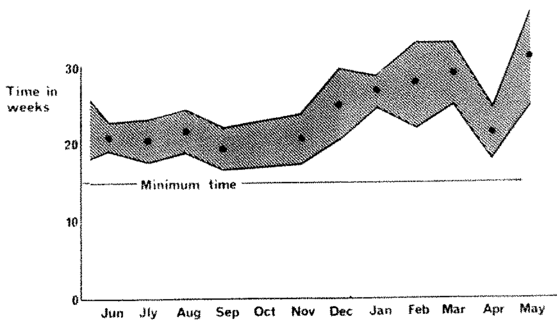
SWINTON N. W., CLERKIN E. P. and FLINT L. D. (1972) Hypercalcemia and familial pheochromocytoma. *Ann. Intern. Med.* **76**, 455–457.

THRALL H. S., FREITAS J. E. and BEIERWALTES W. H. (1978) Adrenal scintigraphy. *Semin. Nucl. Med.* **3**, 23–42.

VAQUEZ H. and DONZELOT E. (1926) Les crises d'hypertension artérielle paroxystique. *Presse Méd.* **34**, 1329–1331.

WELBOURN R. B. (1977) Operations on the adrenal glands. In: ROB C., SMITH R. and DUDLEY H. A. F. (ed.) *Abdomen: Operative Surgery*, 3rd ed. London, Butterworths, pp. 403–419.

Paper accepted 15 February 1979.



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Pancreatogram changes in patients with calculous biliary disease

A. T. R. AXON, M. G. ASHTON AND D. J. LINTOTT*

SUMMARY

A successful pancreatogram was obtained at endoscopic retrograde cholangiopancreatography (ERCP) in 53 patients with calculous biliary disease. Twenty-eight patients presented with jaundice and 25 with pain. In both groups there was a high incidence of pancreatogram abnormalities (47 and 48 per cent respectively). These findings demonstrate that the pancreas is often abnormal in the presence of complicated calculous biliary disease even though there may be no recent clinical evidence of pancreatitis and suggest that asymptomatic chronic pancreatitis may be common. The clinical significance of the abnormalities is discussed.

THERE is well-documented evidence that calculous biliary disease is associated with acute pancreatitis (Gillespie, 1973; Kelly, 1974; Waller, 1975; Read et al., 1976; Hermon-Taylor, 1977) but its association with chronic pancreatitis, although reported (James et al., 1974; Read et al., 1976), appears to be less definite and Mallinson (1977) in a recent review article lists calculous biliary disease as a disputed or unconfirmed association of chronic pancreatitis. It is very difficult to estimate how many patients with cholelithiasis develop chronic pancreatitis because, although it is usual to carry out a cholecystogram in patients found to have chronic pancreatitis, it is not normal practice to perform pancreatic tests on patients with uncomplicated gallstones. However, some patients with calculous biliary disease undergo investigation by ERCP which allows assessment of the pancreas. In this paper we have assessed the incidence of abnormal pancreatograms in patients with calculous biliary disease referred for ERCP.

Patients and methods

Patients

During a 2-year period a successful pancreatogram at ERCP was obtained in 53 patients in whom the diagnosis of calculous biliary disease had been established at some stage, i.e. at previous surgery, cholangiography or at ERCP. In many cases (38) biliary calculi were still present.

In 25 patients (group A) upper abdominal pain was the predominant feature and had precipitated referral. The nature of the pain varied from typical biliary colic (11 patients) to pain very suggestive of pancreatitis (7 patients), but in others the pain was atypical upper abdominal discomfort or more severe pain for which extensive previous investigations had failed to reveal a cause (7 patients). Most of the patients in this group could reasonably have had chronic pancreatitis on clinical grounds, especially as 7 had had a previous documented attack of acute pancreatitis. Eighteen patients in this group had had biliary surgery; of these, 10 had had simple cholecystectomy without exploration of the common bile duct. Two had undergone supraduodenal exploration of the common duct and in 1 of these metal dilators had been passed through the sphincter of Oddi. In 4 patients the common duct had been explored transduodenally and sphincteroplasty was performed in 2. Two patients had had their operation more than 15 years previously and operative details were not available. Three operated patients in this group were found to have retained stones.

Twenty-eight patients (group B) presented with jaundice. A number of these also had pain which was, in every case, compatible with biliary colic. There was no clinical suspicion of pancreatitis in any patient of this group and none of them had had a previously documented episode of acute pancreatitis. Three patients had had cholecystectomy and 1 of these had undergone supraduodenal exploration of the common bile duct. In 18 patients a common bile duct stone was found but in 9 calculi were found only in the gallbladder and a transient common bile duct stone was thought to be the most likely explanation of the jaundice, although at the time of examination no stone was seen. One patient with cholelithiasis had stage IV non-Hodgkin's lymphoma which was responsible for the jaundice.

In order to control the pancreatogram reporting, an attempt was made to include a group of patients expected clinically to have normal pancreatograms. It is difficult, in a study of this nature, to identify a 'normal' group because the indications for ERCP are such that patients are referred with either pain or jaundice; as the only symptom of pancreatitis may be abdominal pain, only patients with jaundice can be used as 'normals', but most of these tend to have either calculous biliary disease or pancreatic cancer and so could not be used here. The 'normal' group (group C) therefore comprised 12 jaundiced patients with hepatitis or non-pancreatic neoplasia and in whom, by chance, a technically satisfactory pancreatogram had been obtained during the ERCP undertaken to demonstrate the biliary tree.

Groups D, E, F, G and H are clinical groupings of patients drawn from groups A and B to demonstrate the relationship of clinical factors to pancreatogram abnormality. Group D comprises patients who had not been operated on and who did not have common bile duct calculi at ERCP, it includes patients with gallstones who had had a transient attack of jaundice and who presumably did at one time have a common duct calculus. Group E is made up of patients who are thought never to have had common duct calculi; this group does include patients who had been operated on but none in whom the common bile duct had been explored. These two groups are 'controls' representing the least complicated group of patients in this series.

Group F is made up of the patients found at ERCP to have common duct calculi; Group G consists of those patients previously operated on and Group H those who had received surgical manipulation of the ampullary sphincter. Group J comprises those patients with a previous documented attack of acute pancreatitis.

Methods

ERCP was performed in the conventional way (Cotton, 1977) using a JFB endoscope. All examinations took place in a general radiographic screening room equipped with image intensification. Contrast medium was injected under television control, using sufficient volumes to demonstrate the duct systems without overfilling, and appropriate radiographs were exposed. Urografin 310M (meglumine diatrizoate 65 per cent) (Schering Chemicals Ltd), being suitably concentrated and viscous, was used for the pancreatograms in order to obtain maximum fine branch detail. A dilute contrast medium, Urografin 150 (meglumine/sodium diatrizoate 30 per cent) (Schering Chemicals Ltd), was used for the cholangiograms to avoid 'white-washing' stones.

All 65 pancreatograms were assessed independently by two experienced observers without clinical information. Where there was disagreement the films were reviewed together and a final decision made. Only technically satisfactory pancreatograms were included in this study. A modification of the

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classification of Kasugai et al. (1972) was used to grade the pancreatograms as normal, minimal change or gross change (Ashton et al., 1978). Gross change was diagnosed in the presence of (*a*) irregular dilatation of the main duct in the head and body with or without stenoses or obstruction, (*b*) widespread side branch abnormalities such as dilatation, 'nipped' origins and irregular distribution, (*c*) localized lesions such as cysts or calculi. Minimal change was diagnosed when there was (*a*) calibre irregularity of the main duct confined to the tail or (*b*) focal side branch abnormality involving at least three branches. The word 'change' was used rather than 'pancreatitis' because structural rather than pathological features were assessed, although correlation between the two is likely.

Results

The results are shown in *Table I*. Twelve (48 per cent) of the patients presenting with pain (group A) had abnormal pancreatograms; the clinical details of this group are given in *Table II*. When patients presented with clinical pancreatic pain the pancreatogram was usually abnormal whereas those with atypical pain usually had normal appearances. Thirteen (47 per cent) of the patients presenting with jaundice (group B) had abnormal pancreatograms whereas only 1 of 12 (8 per cent) of the normal group (group C) were reported as showing an abnormality. The clinical features of these groups are shown in *Tables III* and *IV*. The one patient in group C with an abnormal pancreatogram had porta hepatis neoplasia.

Table V shows the findings in groups D, E, F, G, H and J. It can be seen that the continued presence of a common bile duct stone, or a previous operation, was not especially likely to be associated with an abnormal pancreatogram. *Table VI* shows the average age of the patients with normal and abnormal pancreatograms and the average age of the 'normal' group.

Examples of abnormal pancreatograms are shown in *Figs*. 1–5. *Fig*. 1 shows gross abnormalities of the main duct and side branches throughout the gland. *Fig*. 2 shows similar gross changes with filling of a cyst in the body. *Fig*. 3 shows a grossly dilated main pancreatic duct containing a stone. The tail of this gland was intentionally not opacified in order to avoid overfilling of the possibly obstructed duct system. *Fig*. 4 shows slight dilatation of the main duct with side branch abnormalities especially in the tail. *Fig*. 5 shows main duct and side branch changes in all regions in a patient with a common bile duct stone.

Table I: PANCREATOGRAMS IN BILIARY DISEASE

Clinical group	No abnormality	Abnormal	% Abnormal
Group A (pain)	13	12	48
Group B (jaundice)	15	13	47
Group C ('normals')	11	1	8

Table II: CLINICAL DETAILS OF 25 PATIENTS PRESENTING WITH PAIN (GROUP A)

	Pancreatogram	
Type of pain	Normal	Abnormal
Biliary colic	6	5
Pancreatic	1	6
Upper abdominal	6	1
Total	13	12

Table III: CLINICAL FEATURES OF 28 PATIENTS WITH CALCULOUS BILIARY DISEASE PRESENTING WITH JAUNDICE (GROUP B)

Post-cholecystectomy jaundice with retained stones	3
Untreated common bile duct stones	15
Presumed transient common bile duct stone	9
Non-Hodgkin's lymphoma (with gallstones)	1

Table IV: CLINICAL FEATURES OF 12 PATIENTS KNOWN NOT TO HAVE CALCULOUS BILIARY DISEASE PRESENTING WITH PAINLESS JAUNDICE (GROUP C)

'Hepatitis'	8
Cirrhosis	2
Porta hepatis neoplasia	2

Table V: CLINICAL GROUPS

Group	Clinical detail	Normal pancreatogram	Abnormal pancreatogram
D	No operation + no CBD stone at ERCP	7	9
E	No evidence of CBD stone ever	5	10
F	CBD stone present at ERCP	13	11
G	Previous operation	12	9
H	Ampullary dilatation or sphincteroplasty	2	3
J	Previous pancreatitis	2	5

CBD, Common bile duct.

Table VI: AVERAGE AGES OF CLINICAL GROUPS

Group	Average age (yr)
All patients with normal pancreatograms	51
All patients with abnormal pancreatograms	65
'Normal' group	54

Discussion

The interpretation of minor changes of the pancreatogram, observer variation (Reuben et al., 1978) and possible alterations due to ageing (Kizu et al., 1977) may cause problems in assessment. Poor radiographic quality may cause misinterpretation, with possible over-reporting of minor changes. In order to minimize these errors, experienced observers assessed the pancreatograms using criteria which in a previous study had been shown to correlate with Lundh test results (Ashton et al., 1978). In addition a 'normal' group was included in the study and the assessments were made without clinical information. The surprising finding in this series is that pancreatogram abnormalities were present in 47 per cent of all patients in whom there was a history of cholelithiasis. These patients fall into two groups, those who underwent ERCP because of pain and those whose primary symptom was jaundice. Neither of these groups was ideal for a study of this kind. Patients in the first group were sent for ERCP because of difficult pain and in many of them pancreatitis was suspected clinically. The second group was more representative because these were patients who presented with jaundice and in none of them was there any clinical suspicion of pancreatitis before the ERCP was carried out; the 46 per cent incidence of pancreatic abnormality was a surprisingly high finding but it should be emphasized that nearly all the patients in this group probably had common bile duct calculi and so cannot be said to have uncomplicated calculous biliary disease.

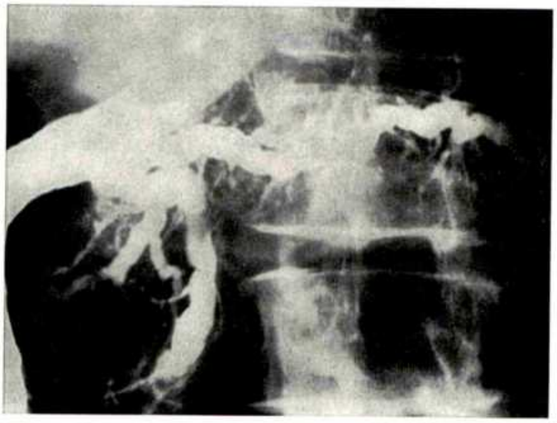


Fig. 1. Pancreatogram of a 62-year-old female referred for endoscopic papillotomy for retained common bile duct stones presenting with jaundice. There is gross abnormality of the whole duct system throughout the gland.

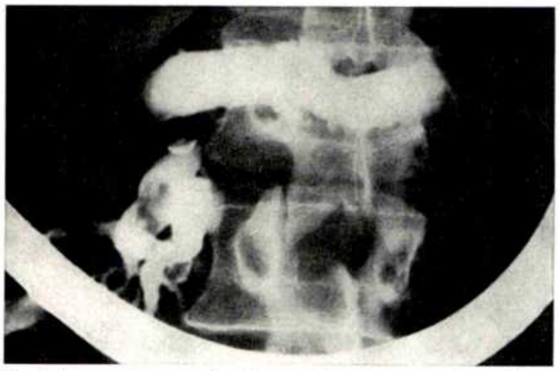


Fig. 3. Pancreatogram of a 42-year-old male presenting with further abdominal pain after cholecystectomy and sphincteroplasty 2 years previously. A stone is present in the main pancreatic duct, which is grossly dilated.

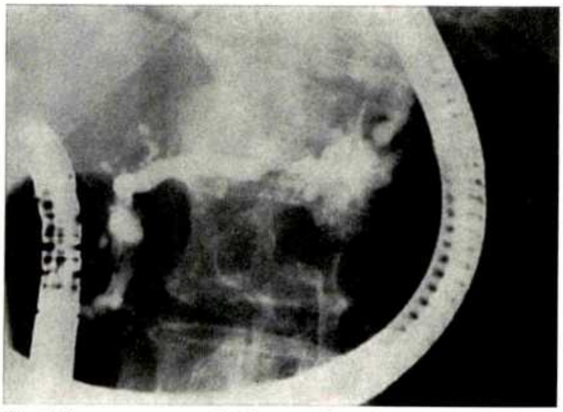


Fig. 2. Pancreatogram of a 70-year-old male presenting with pain and an episode of acute pancreatitis after cholecystectomy. No retained stones were seen. There is a cyst in the body of the gland with gross changes of the main duct and side branches.

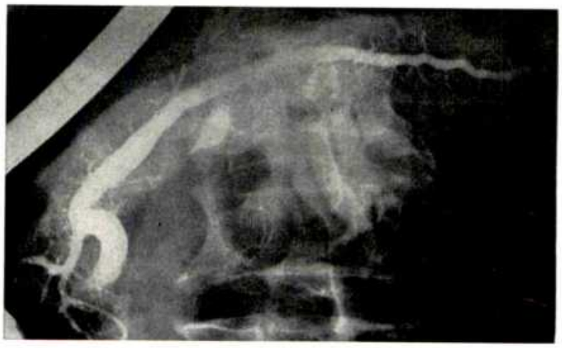
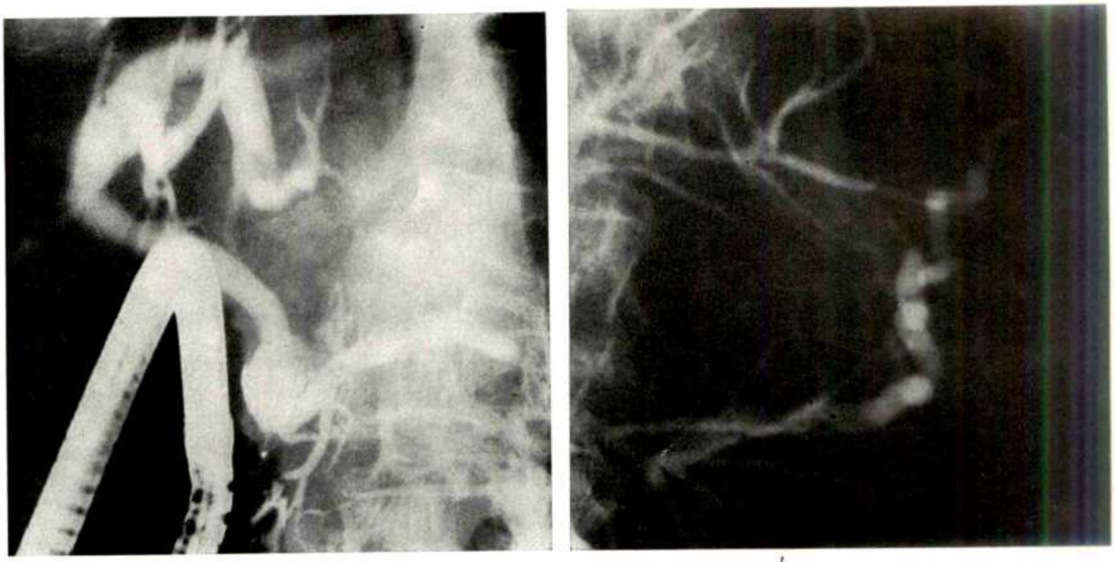


Fig. 4. Pancreatogram of a 70-year-old male presenting with jaundice due to a common bile duct stone. The main pancreatic duct is slightly dilated and the side branches, particularly in the tail of the gland, are abnormal.

The clinical significance of these changes is speculative. The effect of age upon the pancreatogram is not clearly defined, the results of necropsy studies (Kizu et al., 1977) differing from those of studies *in vivo* (Kasugai et al., 1972; Varley et al., 1976). The patients with abnormal pancreatograms were on average older than both the patients with normal pancreatograms and those in the control group (*Table VI*). However, if pancreatic disease is related to biliary disease then more severe changes are to be expected in those patients who have had biliary disease the longest. Furthermore, in many patients the severity of the pancreatogram changes, some of which have been illustrated, makes it unlikely that age alone is responsible.

The diagnosis of chronic pancreatitis rests upon the demonstration of irreversible structural, functional or microscopic abnormality in the gland. Pancreatography is a relatively crude method of assessing parenchymal damage as interpretation depends upon changes in the first and second order ducts only, and it may be that this had led to an underestimation of the incidence of pancreatic disease. One patient whose pancreatogram was reported normal in this series underwent laparotomy for gallstones a few weeks later and at operation was found to have extensive chronic pancreatitis in addition to gallstones. It is clear from the illustrations that a number of the patients reported here have abnormalities of the pancreatic ducts which represent advanced and widespread chronic pancreatitis which, in some cases, was asymptomatic. Other patients had relatively minor changes whose significance is open to question. These findings may represent a spectrum of disease ranging from the severe to early, possibly non-progressive, or even reversible disease.

If it is accepted that the pancreatogram changes demonstrated here do represent stages in the evolution of chronic pancreatitis it is interesting to speculate whether the presence of a stone in the common bile duct is the factor that triggers the event. Ten patients had undergone surgery for gallstones without exploration of the common bile duct. It seems reasonable to suppose that in these there was no preoperative suspicion of common duct calculi; only 1 of these patients was found to have a common duct calculus at ERCP. A further 6 patients had not been operated on and had never had symptoms or investigations to suggest a common duct calculus. It seems likely then that 15 patients had never had common duct calculi



a *b*

Fig. 5. Pancreatogram of a 74-year-old female presenting with jaundice due to a common bile duct stone. The main pancreatic duct is dilated and there are abnormal side branches throughout.

(group E, *Table V*). Of these, 5 (33 per cent) were found to have an abnormal pancreatogram; this suggests that the presence of a common duct calculus is not necessary for the development of chronic changes in the pancreas, although it is possible that these 5 patients might have had silent common duct calculi which had passed spontaneously.

What is the effect of a previous operation? Twenty-one patients had been operated on for gallstones and of these, 5 had received attention to the ampulla of Vater—either dilatation or sphincteroplasty; *Table V* shows that abnormal pancreatograms were found in 43 per cent of those operated on, and of the 5 whose ampullary sphincter had been interfered with, 2 were normal and 3 abnormal. It is not known whether the pancreatogram changes antedated the operation or whether they had occurred since and the numbers are too small to draw conclusions as to whether ampullary surgery affects the pancreatogram. What does emerge from these figures however is that patients continue to have pancreatogram changes and symptoms of pancreatitis following apparently successful biliary surgery and in the absence of common duct calculi.

These findings raise two important clinical questions. The first of these relates to the differential diagnosis of upper abdominal pain and the difficult problem raised by the new investigation of ERCP which may demonstrate ductal abnormalities in the presence of biliary disease. Should the biliary disease and the pancreatic disease be treated at the same time? It should be emphasized that pancreatograms merely demonstrate an abnormality in the pancreatic duct system, and do not establish the diagnosis of clinical pancreatitis. It is salutary that half the patients with abnormal pancreatograms in this series were asymptomatic as far as the pancreas was concerned; they presented with jaundice. Several of the patients who presented with pain and had abnormal pancreatograms had another lesion as well; 5 of the 12 had biliary calculi at the time of ERCP, a more likely cause of pain. Therefore the presence of an abnormal pancreatogram in the remaining 7 does not necessarily mean that this was the cause of the pain. In view of the generally poor results of conservative pancreatic surgery and the high complication rate of all pancreatic surgery, when biliary and pancreatic disease coexist it is probably wiser to tackle the biliary tract and leave the pancreas alone.

Secondly, should surgery be undertaken on the basis of duct abnormalities shown at pancreatography? Very little data are available to answer this question adequately. There is no consensus as to which operation should be carried out for generalized gross pancreatic disease, and what is needed is a randomized prospective trial comparing surgery carried out on the basis of anatomy with a standard radical operation. It must be emphasized that the indication for operative treatment is clinical and that medical treatments, alcohol withdrawal and, where indicated, biliary surgery should be exhausted before resorting to pancreatic surgery, and only then if symptoms are severe.

Finally, it should be emphasized that this series of patients is a highly selected group; uncomplicated patients with calculous biliary disease are not usually referred to ERCP. The high proportion of patients with abnormal pancreatograms suggests that mild or subclinical pancreatitis is very common in biliary disease but further work is needed to confirm these findings and to discover why, in some patients, probably the vast majority, the pancreas can be disorganized without causing symptoms, while in others with severe incapacitating disease there may be little or no change in the pancreatogram.

References

ASHTON M. G., AXON A. T. R. and LINTOTT D. J. (1978) The Lundh test and ERCP in pancreatic disease. *Gut* **19**, 910–915.

COTTON P. B. (1977) Progress report: ERCP. *Gut* **18**, 316–341.

GILLESPIE W. J. (1973) Observations on acute pancreatitis: a post mortem review. *J. R. Coll. Surg. Edinb.* **20**, 36–41.

HERMON-TAYLOR J. (1977) An aetiological and therapeutic review of acute pancreatitis. *Br. J. Hosp. Med.* **18**, 546–551.

JAMES O., AGNEW J. E. and BOUCHIER I. A. D. (1974) Chronic pancreatitis in England: a changing picture? *Br. Med. J.* **2**, 34–38.

KASUGAI T., KUNO N., KOBAYASHI S. et al. (1972) The normal endoscopic pancreatocholangiogram. *Gastroenterology* **63**, 217–226.

KELLY T. R. (1974) Gallstone pancreatitis. *Arch. Surg.* **109**, 294–297.

KIZU M., NEWMAN J., COTTON P. B. et al. (1977) Histological correlations with pancreatography in necropsy specimens. *Gut* **18**, 399–400.

MALLINSON C. (1977) Chronic pancreatitis. *Br. J. Hosp. Med.* **18**, 553–567.

READ G., BRAGANZA J. M. and HOWAT H. T. (1976) Pancreatitis—a retrospective study. *Gut* **17**, 945–952.

REUBEN A., JOHNSON A. L. and COTTON P. B. (1978) Is pancreatogram interpretation reliable? A study of observation and error. *Br. J. Radiol.* **51**, 956–962.

VARLEY P. F., ROHRMANN C. A., SILVIS S. E. et al. (1976) The normal endoscopic pancreatogram. *Radiology* **118**, 295–300.

WALLER S. L. (1975) *The Aetiology of Pancreatitis. Topics in Gastroenterology.* Oxford, Blackwell Scientific, pp. 79–116.

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Chronic relapsing pancreatitis: a review of 64 cases

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SUMMARY

A collected series of 64 cases of chronic relapsing pancreatitis is reported. Analysis of this material reveals several points of interest. There is a difference in the aetiological spectrum in Britain when compared with reports from France and the United States. In particular, nearly half the British cases were idiopathic. The clinical presentation and the age and sex ratios also varied with aetiology. Endoscopic retrograde cannulation of the pancreatic duct was of little value in confirming a diagnosis of pancreatitis in the problem case. This investigation did, however, demonstrate that a widespread dilatation of the pancreatic duct was a minority finding. In those patients with alcoholic pancreatitis follow-up studies have shown that, if the addiction can be broken, there is a 75 per cent chance that pain will diminish or disappear with the passage of time. The main indication for surgical intervention was severe pain and this study has shown that if strict criteria are observed, a worthwhile relief of symptoms can be achieved. In particular, subtotal pancreatectomy produced good results in up to 85 per cent of cases, although with an appreciable short term postoperative morbidity.

CHRONIC relapsing pancreatitis is still an uncommon condition in the United Kingdom. Experience in the management of the disease must therefore be drawn from collected series of cases and the present report is based on a group of patients referred for surgical treatment over a period of 15 years.

Patients and methods

Between 1961 and 1976, 64 patients with chronic relapsing pancreatitis have been collected. The majority were seen in the past 8 years. There is a minimum follow-up of 1 year with a mean of 5·5 years for all cases. There were 3 deaths in this series attributable to the disease.

The patients were either referred to a surgical outpatients clinic by general practitioners and local consultant colleagues (43 cases) or from other centres for specific consideration of surgical treatment (19 cases). They must therefore be regarded as having been selected because of their possible need for surgery.

Diagnosis

The diagnosis of chronic relapsing pancreatitis was accepted on a combination of clinical, biochemical and radiological findings.

A clinical diagnosis was made on various criteria:

1. A history of a typical attack of acute pancreatitis, with biochemical or operative confirmation, which then drifted on into a chronic relapsing pattern.
2. A patient presenting with typical pain and a history of alcoholism, with or without diabetes, and radiological evidence of pancreatic calcification.
3. Clear evidence of exocrine and endocrine insufficiency, with or without calcification, with or without abdominal pain.
4. Upper abdominal pain 'of pancreatic type' alone.

This last group presented the greatest diagnostic difficulty, for it is now well recognized that it is all too easy to label a patient as suffering from 'pancreatitis' simply because no other cause for his pain can be identified. It is therefore in this group of cases that one looked specifically to the laboratory and the X-ray department for special help.

A raised serum amylase in acute pancreatitis—and a further elevation during a relapse—is clearly of value. Biochemical confirmation of steatorrhea or diabetes is also significant. Apart from this, experience with the present series has shown that the laboratory has little to offer in establishing a diagnosis of chronic relapsing pancreatitis *in the problem case*. Seven patients were referred for intubation and secretin tests. In 4 instances the results were within the normal range. In 2 patients the findings were equivocal and in the remaining case the test was 'unsatisfactory due to difficulty with positioning of the tube'. Of these 7 cases, 6 had the diagnosis confirmed subsequently by other means, while in the remaining patient whose test was normal, it soon became apparent that he had a carcinoma of the body of the pancreas.

Radiological evidence of pancreatic calcification was only detected in 9 of these 64 cases. It was therefore a rare occurrence even in the subgroup with alcoholic pancreatitis. Barium meal examination was performed in 38 patients, usually to exclude peptic ulcer disease. It was useful in the diagnosis of a pancreatic pseudocyst on 5 occasions and confirmed the presence of gastro-oesophageal varices in 1 patient, but in this survey it did not contribute to the primary diagnosis of pancreatitis in any instance.

In the past 3 years, ultrasonography has proved very useful in the detection of the complications of pancreatitis and especially in localization of a pseudocyst. Experience in the use of this diagnostic tool as a means of delineating an enlargement of the pancreas itself is still limited, but in 3 recent cases preoperative assessment by this method correlated remarkably well with the operative findings.

Thirty-one patients underwent endoscopic retrograde cannulation of the pancreatic duct (ERCP). Analysis of the X-rays has revealed two points of interest. First, the ERCP was only of definitive diagnostic value in 6 patients. In the remainder the diagnosis was already clear or the ERCP findings were equivocal. Secondly, only 4 of the 31 cases showed a typical segmental dilatation of the duct of Wirsung—the 'chain of lakes' appearance. A duct of normal calibre was a much commoner finding in this series of cases even when the disease was macroscopically severe.

Eight patients were referred for treatment of 'pancreatitis' with the diagnosis resting to a large extent on minor changes on an ERCP. In 3 instances the pancreas was completely normal at operation. In 5 other patients a quite different cause for the pain was found: in 4 cases there was a peptic ulcer and the fifth patient had a carcinoma of the pancreas. None of these 8 patients is included in the present report but they require mention to emphasize that ERCP alone is of limited value in diagnosis, particularly when the changes are of a minor variety.

It is perhaps a commentary on the difficulty experienced in the diagnosis of chronic relapsing pancreatitis that in this small group the diagnosis was only made at the time of initial assessment in half the patients. In the remainder it emerged over a period of 6 months to 6 years during regular follow-up reviews, either because of some change in one of the biochemical or radiological parameters or because the patient's pain became so bad that surgical intervention was required. In spite of the use of a wide variety of investigations, in 8 patients the diagnosis was only finally established at laparotomy.

Aetiology

The 64 patients divide naturally into two groups (*Table I*). In 33 patients there was a clear history of alcoholism with an intake of spirits in excess of 400 ml per day or the equivalent in wine or beer. No clear aetiological factor could be uncovered in the remaining 31 patients; 4 had undergone cholecystectomy but only one of these patients actually had biliary tract disease—a solitary stone in a functioning gallbladder—and the operation

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Table I: CLINICAL PRESENTATION OF 64 CASES OF CHRONIC RELAPSING PANCREATITIS

Aetiology	Age (yr) Range	Av.	Sex M	F	Presentation A	I	Calcification on X-ray
Alcoholic	18–53	43	30	3	32	1	5
Idiopathic	12–75	49	11	20	15	16	4

Av., Average; A, acute, I, insidious.

Table II: EFFECT OF CONTINUING ALCOHOLISM ON PROGNOSIS

	Total	Pain persisting	Pain-free
Drinking	10	8 (4)	2 (1)
Stopped	17	4 (1)	13 (2)

Figures in parenthesis indicate patients who had undergone surgery.

performed in 1964 had not altered the patient's symptoms in any way. All of this group were screened for biliary tract disease, hypercalcaemia and hyperlipidaemia. Also, a most careful inquiry was made via the general practitioner and relatives into each patient's drinking habits so as to exclude alcoholism. It is therefore necessary to place these 31 cases in an 'idiopathic' group.

The presentation and prognosis of these two groups differed and they will be presented separately.

Alcoholic group (33 patients)

Sex and age: Thirty of these patients were men. The average age was 43 years, the oldest patient was 53 and the youngest, who had been drinking half a bottle of gin a day for 5 years, was 18. The majority of cases (25) were in their thirties or forties.

Presentation: Thirty-two of these 33 patients presented with a typical attack of acute pancreatitis and then, as they continued drinking, their clinical symptoms progressed to a chronic relapsing pattern of the disease. In only one instance in this group was the onset insidious.

By the time the diagnosis of pancreatitis was established, 4 patients were found to be diabetic: only 5 showed radiological evidence of pancreatic calcification.

Progress: There were no deaths due to pancreatitis in this group. One patient, however, died during the follow-up period. When first seen in 1961, the patient, aged 42 years, was known to be a severe chronic alcoholic who had been in the habit of taking 18 pints of beer plus one bottle of whisky a day for at least 10 years. He was admitted to hospital for investigation and treatment of a peripheral neuritis but for the preceding 4 years he had suffered recurrent attacks of abdominal pain of varying degrees of severity. Investigations had failed to reveal the cause. While in the ward he developed a further severe attack and a serum amylase of 4250 Somogyi units was noted. Following a stormy illness, the patient recovered and was apparently persuaded to stop drinking. Over the succeeding 2 years, his abdominal symptoms settled and his peripheral neuritis improved, but in 1964 a diagnosis of hepatic cirrhosis was made and this progressed, with the development of ascites, until in 1966 he was readmitted in hepatic pre-coma. He responded to treatment at that time but eventually died of liver failure in 1968. Autopsy confirmed the presence of chronic liver disease; the biliary tract was normal; the pancreas was shrunken and fibrotic.

Five patients in this subgroup of alcoholic pancreatitis were lost to follow-up. In the remaining cases (27 patients) the progress of the disease appeared to depend on whether or not the patient was able to break his addiction (*Table II*). Of the 10 patients who admitted to continued drinking, 8 still had considerable pain in spite of the fact that 4 had undergone some form of surgery. Of the 2 patients who were pain-free—following subtotal pancreatectomy in one—and who were still drinking, it may be significant that their habits had changed. Instead of imbibing half a litre of spirits a day, they were now content with 2 pints of British beer!

By contrast, 17 patients had managed to break their addiction. It is accepted that this is a sensitive area because a patient's story may be most unreliable but each claim was checked with relatives and with the general practitioner. However, the clinical status of these cases differed quite significantly from those who admitted that they were still drinking: 13 patients said they were pain-free, although 2 may have benefited from surgery; 4 patients still had pain, in spite of operation in one case, but 3 of this group were back at work. It is also an interesting feature that in this subgroup those who still had symptoms said that these were lessening with the passage of time, and when seen for follow-up, no patient required regular analgesics.

From an overall view of these cases of alcoholic chronic relapsing pancreatitis, it may be concluded that, if a patient can stop drinking, he has a 75 per cent chance that his symptoms will settle.

Idiopathic group (31 patients)

Sex and age: The sex/age pattern differed in two respects from the previous group. There was a reversal of the sex incidence—only 11 of the 31 cases were men—and the age range was much wider (12–75 years). The average age was 49 with a much more even spread over the years.

Presentation: Only 15 of these 31 patients experienced an initial attack of acute pancreatitis; in the remainder the onset was insidious. Three patients had clear evidence of exocrine and endocrine insufficiency and one of these also showed radiological evidence of calcification. Three other patients also presented with pancreatic calcification.

Progress: There were 3 deaths in this group attributable to pancreatitis. The first fatality occurred in a girl who began to have attacks when she was 13 years old. By the age of 18 she had suffered 11 episodes of pain severe enough to require admission to hospital. A cholecystenterostomy had been performed when she was 14 with no benefit and a distal pancreatectomy with Roux-en-Y drainage (Duval's operation) at the age of 16 years. This gave a remission of her symptoms for 18 months but then the relapses began again. In her final attack she was admitted with severe pain and hypotension. On this occasion she did not respond to resuscitation and died within 48 h in 'irreversible shock'. A careful autopsy revealed only severe chronic pancreatitis affecting the residue of the gland. The Roux loop had healed and separated from the tail of the pancreas. There was minimal fat necrosis but no haemorrhagic or necrotic change in or around the gland.

The second fatality occurred in a lady aged 67. In 1952 a diagnosis of pancreatitis was established at laparotomy when, during a severe illness, a pancreatic abscess was drained and a cholecystostomy performed, even though there was no evidence of any biliary tract disease. The patient then had further recurrent attacks of pain with several admissions to hospital. Between these relapses she suffered increasing chronic upper abdominal symptoms. In 1963 as an elective procedure her abdomen was re-explored. The biliary tract was normal but the gallbladder was removed. The pancreas was noted to be very hard, enlarged and irregular. The body was therefore transected with a view to performing a Peustow procedure but the duct of Wirsung was of normal calibre. The tail of the pancreas and the spleen were therefore removed and the stump of the gland was oversewn. The patient remained well for 72 h but then her condition deteriorated rapidly and she died. At autopsy the cause of death was found to be a *Clostridium welchii* septicaemia, gas being present in the liver. The pancreas was fibrosed but there was no active disease and no evidence of carcinoma. It was noted that the duct of Wirsung and the common duct opened separately into the duodenum.

The third patient who died was a woman aged 52. The initial diagnosis of pancreatitis had been made at laparotomy in 1954. There was no evidence of biliary tract disease at that time. Over the succeeding 8 years the patient was readmitted five times with severe pain but, in addition, she complained of increasing upper abdominal discomfort even between her relapses. First a left perinephric abscess was drained and then, 3 weeks later, at a further exploration a subphrenic abscess was also drained. In spite of this, the patient's condition failed to improve, she deteriorated and eventually died in coma. At post-mortem examination death was found to be due to a staphylococcal meningitis. The pancreas was small and fibrotic with little normal tissue remaining, but in spite of this the patient had never developed diabetes or steatorrhoea during life.

The 28 survivors in this idiopathic group have all been traced and reviewed. Three patients have minimal abdominal symptoms, their main problem being pancreatic insufficiency, which is being managed medically. Of the remaining 25 cases, 11 were found to have mild symptoms of remission and relapse but these were not severe enough to prevent them working normally. There were, however, two features which caused some concern. In nearly all patients there seemed to be a tendency for the pain to be increasing with the passage of time and also serial intravenous cholangiograms have demonstrated a progressive dilatation of the common bile duct in half of this group.

The other 14 patients all had severe pain sufficient to stop them working and to disrupt their lives. It is these patients, as well as some of those with alcoholic pancreatitis, who were considered for surgery.

Surgical treatment

Indications: Surgical intervention was required for two main reasons. In the first place, operation was performed to deal with one of the complications of the pancreatitis such as pseudocyst (5 patients), pancreatic abscess (2 patients) and haematemesis due to splenic vein thrombosis producing gastric varices (1 patient). Secondly, and this was the overwhelming indication, surgery was performed in an attempt to alleviate crippling pain.

Apart from the interventions for pancreatic abscess, operation was always undertaken circumspectly with a considerable period of preoperative assessment. In particular, this has become our policy in patients where an operation is to be undertaken for pain. All patients have been admitted to hospital so as to allow careful observation of the severity of their symptoms and a special record is kept of their analgesic requirements. In some instances, sterile saline injections were substituted for variable periods in order to confirm the genuineness of the patient's symptoms. Home background and the personality of the patients are now studied routinely so as to build up as complete a picture as possible, as dependability of character has proved to be most important in the postoperative management. It is also our practice to stress to the patients the drawbacks of surgery and especially of pancreatic resection if this is under consideration, so as to deter them from operation if possible; this is done in the knowledge that the patient will return and ask for operation if the pain is sufficiently severe. This careful screening has resulted in rejection of several patients who had been specifically referred for operation from other centres, either because it was felt that their symptoms were not in fact arising from the pancreas or because, even though there was some evidence of disease of the gland, the period of observation and our investigations suggested that this was not the main cause of their pain. In the event, only 26 of the 64 patients originally referred for a surgical opinion have so far undergone operation.

Results

Surgery for complications

Five patients required surgery on account of pseudocyst formation. An internal drainage into the stomach was performed and in each instance the short term effect was good. In particular, there was complete relief of pain. However, on longer follow-up, the pain has recurred in 4 out of 5 cases. Two patients have required further surgery at 2 years and 5½ years after drainage, while in the other 2—followed now for 4 and 11 years respectively—the pain is not sufficiently severe to merit a further operation at present. Only 1 of the 5 cases undergoing pseudocyst drainage remains symptom-free at 3 years. An ERCP has been performed on 3 of the 5 patients, one prior to reoperation, and there was no sign of any patency of the internal drainage. In the 2 patients undergoing further surgery, there was no reaccumulation of the cyst nor any direct connection between the stomach and the pancreas.

Two patients required drainage of a pancreatic abscess: one recovered and the other died.

One man who was having small haematemeses regularly every 3–4 months over a period of 4 years underwent a splenectomy 4 years ago and has remained completely symptom-free.

Surgery for control of pain

Three surgical approaches were used in this group of patients. *Biliary drainage procedures*: In the early years of the present series, 7 patients underwent various biliary tract operations, including sphincteroplasty in 3 instances, but in no case was there any lasting benefit. Only one of these patients actually had biliary tract disease—a solitary stone in a functioning gallbladder. Four patients have required further operations in an attempt to control their pain.

Drainage of the pancreatic duct: This was performed in 7 patients. A simple amputation of the tail with anastomosis to a Roux loop (Duval's procedure) was carried out in the girl already mentioned who subsequently died. In the remaining 6 patients either a filleting with invagination (Puestow, 2 cases) or a laying open of the pancreatic duct with a Roux loop onlay *in situ* (4 cases) was performed. All these patients did well initially and obtained relief of their pain in the short term, but on follow-up only 1 of the 6 survivors, a girl of 13 who is now 19, has remained symptom-free, although she has become diabetic. Three patients have required a re-exploration and subtotal resection of the pancreas and it is interesting that on each occasion when the pancreas was exposed, it was found that the Roux loop had healed and separated completely from the gland. The remaining 2 cases have smouldering symptoms; one is an alcoholic who continues to drink.

An ERCP has been performed on the girl who is symptom-free and on 2 patients who still have symptoms but have not required re-exploration. It has not been possible to demonstrate any patency of an anastomosis between the duct of Wirsung and the Roux loop in these 3 patients.

This finding, taken together with the ERCP findings in the pseudocyst patients, leads one to question the long term effectiveness of internal drainage procedures.

Pancreatic resection: An 85–95 per cent resection by the technique recently described (Trapnell, 1978) was performed in 15 cases, all of whom had a small-calibre pancreatic duct. The clinical data for these cases are set out in *Table III*. There was no mortality but high morbidity. Six patients suffered prolonged septic complications and in one of these there was also haemorrhage from the pancreatic bed, requiring multiple transfusions. Four patients in this group were diabetic preoperatively and a further 4 were rendered diabetic by the operation, but it is interesting that in 7 patients who did not become diabetic, 4 had macroscopic disease which was as severe as any in the whole series. Weight change was not a feature in the majority of the cases in this series. Only 2 patients increased their weight significantly postoperatively

Table III: CLINICAL DATA—PREOPERATIVE AND AT FOLLOW-UP—FOR 15 CASES UNDERGOING SUBTOTAL PANCREATECTOMY

Case	Sex	Date of birth	Alcoholic	Operation	Complications	Diabetic		Weight (kg)		Pain status at FU
						Preop.	FU	Preop.	FU	
E. G.†	F	1913	Yes	1967	Abscess	No	No	58	61	90% improved
G. McD.†	M	1921	Yes	1967	—	Yes	Yes	86	84	80% improved
A. G.†	M	1921	Yes	1968	—	No	Yes	82	85	Pain-free*
C. G.	F	1926	Yes	1968	—	No	No	61	66	50% improved
S. P.	F	1933	No	1971	Abscess	No	No	63	62	Pain-free
T. C.	M	1920	No	1971	Abscess	No	Yes	72	77	Pain-free
R. B.	M	1928	No	1972	Abscess	No	No	59	76	Pain-free
P. L.	F	1920	No	1972	—	No	Yes	54	56	90% improved
I. A.	F	1933	No	1974	—	No	No	86	70	Pain-free
N. S.	M	1947	Yes	1974	Abscess and haemorrhage	Yes	Yes	56	69	40% improved
N. M.	M	1926	Yes	1974	—	No	No	83	80	Pain free*
J. T.	M	1942	No	1975	Abscess	Yes	Yes	82	86	Pain-free
S. P.	F	1938	No	1975	—	No	Yes	63	67	Pain-free
A.D.	M	1928	No	1975	—	No	No	72	69	Pain-free
F. G.	M	1930	Yes	1976	—	Yes	Yes	87	90	50% improved

FU, Follow-up.
* Patients have stopped drinking.
† These 3 patients were last seen for follow-up in 1975.

(R. B. and N. S.) while one lady (I. A.), who needed to diet, lost 16 kg (*Table III*).

The result of this operation must be judged on its ability to relieve pain. Follow-up studies show that all patients were improved; 9 say they are completely pain-free, 3 have a mild indigestion which they can control by limiting their diet, their life not being affected in any other way. In 3 patients there is an improvement in pain but not sufficient to allow them to return to their work. Two of these cases have a considerable inadequacy of personality which has made management difficult and the control of alcoholism impossible. However, a significant and useful reduction in analgesic requirement has been achieved in each case following operation.

Discussion

In the past 5 years major series of chronic relapsing pancreatitis treated surgically have been reported from Seattle (White and Keith, 1973), Paris (Leger et al., 1974), Michigan (Frey et al., 1967) and Houston (Jordan et al., 1977). When these reports are compared with the present study and also with the review of James et al. (1974), it is apparent that chronic relapsing pancreatitis is still relatively uncommon in the United Kingdom and also that the aetiological pattern is different. In particular, the alcoholic form of the disease is not nearly as common in this country as in North America. In a search for some other cause all patients were screened for hyperparathyroidism and hyperlipidaemia. Biliary tract disease was excluded but other studies (Trapnell, 1966) have shown that gallstone pancreatitis only very rarely progresses to the chronic relapsing form of the disease. It is also notable that with the larger proportion of idiopathic cases available in the present study, an apparently significant variation in presentation between this group and those with alcoholic pancreatitis has emerged. This has not been commented on in previous reports.

The exact incidence of chronic relapsing pancreatitis in Great Britain is not known, for no geographic survey has as yet been published in this country. However, it is interesting that in the course of a 20-year survey in Bristol which yielded 590 cases of acute pancreatitis (Trapnell and Duncan, 1975) a search of hospital records produced just 61 patients coded as suffering from chronic or chronic relapsing disease. Examination of these patients' records showed that only 33 of them met the present diagnostic criteria for chronic relapsing or chronic pancreatitis (Trapnell, 1969). Furthermore, the majority of the 33 patients were pain-free and presented mainly for medical investigation.

The slow and sequential management of the condition is a feature which has emerged during the experience of this series of patients. In a disease characterized by remission and relapse there need be no rush into surgery unless complications develop; when these do occur they can be dealt with on their merits. The present study confirms the view of others (Frey et al., 1976; Jordan et al., 1977) that a conservative policy should be maintained for as long as possible and for several reasons. If surgery is eventually required it may be major and extensive, particularly if a resection is needed. These patients are often in poor general condition due to anorexia and malnutrition. This may result from the severity of their pain alone, but if they are alcoholic as well this often makes them unreliable in their care of themselves. Indeed, 4 patients in this section were verging on becoming vagrants and this accounted for loss in follow-up in this group. Also there may be other diseases secondary to the alcoholism which will complicate the management of the pancreatitis still further, such as peptic ulceration and hepatic cirrhosis.

Then again it has already been stressed that the pain which has been attributed to pancreatitis may not be arising from this cause but from some other condition, or indeed that it may not be organic at all, and both these possibilities add further weight to a policy of conservatism. The longer operation is delayed, the more opportunity there will be to assess these various aspects. Frey et al. (1967) now refer all their patients for psychiatric assessment preoperatively and they have concluded that operation is absolutely contraindicated, however definite the diagnosis and however severe the symptoms, in anyone who is severely depressed or who has suicidal tendencies.

The results of surgical treatment in this series have been variable. The number of cases undergoing drainage of a pseudocyst or pancreaticojejunostomy are too small to allow any real comparison with other reports, but even so the follow-up studies, particularly for pancreaticojejunostomy, are disappointing. This poor showing, especially when compared with the experience of others, would suggest that our criteria of selection for the operation were incorrect. White and Keith (1973), in a large series of patients, found after a mean follow-up of 4½ years that 46 per cent of their patients were symptom-free: 35 per cent had improved. The results from Paris (Leger et al., 1974) were similar, approximately half of the patients followed over a 20-year period being relieved of pain. Jordan has achieved even better results with the same operation (Jordan et al., 1977). He found that 90 per cent of his 25 patients were pain-free. Indeed, as his results are so much better than those of others this would seem to suggest that his criteria of selection were very strict, thus producing his excellent success rate. The finding of a healed Roux loop in the patients who were re-explored is of some interest and the postoperative ERCP assessment of the other patients also suggests that a pancreaticojejunal anastomosis may close off spontaneously. However, this anastomotic closure is not necessarily related to a recurrence of the patient's symptoms. This finding must lead to further speculation as to the role of duct blockage and dilatation as a primary cause of the disease and of the patient's symptoms.

The results for subtotal pancreatectomy obtained for the present series of cases—an 85 per cent relief of pain—are comparable with the findings in the other major reports of this operation (Leger et al., 1974; Frey et al., 1976). It is also interesting that both these other groups, while having no mortality, also experienced a high postoperative morbidity.

Clearly, patients with chronic relapsing pancreatitis are difficult to manage, but some surgical guidelines are beginning to emerge. When operation is required, the procedure should be tailored to the site of the pancreatic disease and, in particular, to the state of the pancreatic duct. Then, on strict criteria, it would appear that operation can benefit those patients with severe pain. This is the only option open in cases of idiopathic pancreatitis where symptoms continue to worsen. For the alcoholic, however, the long term prognosis still depends primarily on whether or not he can break his addiction. If this is possible, then there is a 75 per cent chance that operation will not be required while, if the patient continues to drink, operation may give him some benefit for a while. Eventually his pain is likely to return and, more particularly, he is likely to die of the other complications of chronic alcoholism.

References

FREY C. F., CHILD C. G. and FRY W. (1976) Pancreatectomy for chronic pancreatitis. *Ann. Surg.* **184**, 403–413.

JAMES O., AGNEW J. E. and BOUCHIER I. A. D. (1974) Chronic pancreatitis in England: a changing picture? *Br. Med. J.* **2**, 34–38.

JORDAN G. L., STRUG B. S. and CROWDER W. E. (1977) Current status of pancreatico-jejunostomy in the management of chronic pancreatitis. *Am. J. Surg.* **133**, 46–51.

LEGER L., LENRIOT J. P. and LEMAIGRET G. (1974) Five to twenty year follow-up after surgery for chronic pancreatitis in 148 patients. *Ann. Surg.* **180**, 185–191.

TRAPNELL J. E. (1966) The natural history and prognosis of acute pancreatitis. *Ann. R. Coll. Surg. Engl.* **38**, 265–287.

TRAPNELL J. E. (1969) Unpublished data.

TRAPNELL J. E. (1978) Operative techniques—subtotal pancreatectomy. *Br. J. Hosp. Med.* **19**, 482–491.

TRAPNELL J. E. and DUNCAN E. H. L. (1975) Patterns of incidence of acute pancreatitis. *Br. Med. J.* **2**, 179–183.

WHITE T. T. and KEITH R. G. (1973) Long term follow-up study of 50 patients with pancreatico-jejunostomy. *Surg. Gynecol. Obstet.* **136**, 353–358.

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Bile composition and osmolarity in the interpretation of formation of bile stones and their classification

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SUMMARY

We studied the bile and gallstone composition of 38 surgical patients. According to their composition, the stones were classified as: 1, cholesterol stones, when they have more than 60 per cent cholesterol, or 2, pigment or pigment-mixed stones, when they have more than 40 per cent pigments (including stones with more than 30 per cent calcium). In the cholesterol-stone-forming group (24 cases) a 'supersaturation' in the cholesterol component of the bile and a concomitant reduction in bile salts was found. No such bile supersaturation was found in those with pigment or pigment-mixed stones (14 cases), or in the control group (8 cases).

The osmolarity of bile in patients with pigment or pigment-mixed stones is significantly higher than in those with cholesterol stones or in controls.

These results suggest a different mechanism for gallstone formation in the two groups: a 'supersaturation' of cholesterol with respect to bile salts and phospholipids in the formation of cholesterol stones and an 'overconcentration' of all bile components as a whole in the formation of pigment stones.

In an attempt to clarify the aetiology of gallstone formation, we measured in the bile of patients operated on for cholelithiasis the following parameters: cholesterol, bile salts, phospholipids and, for the first time, osmolarity. Chemical analysis of the gallstones was conducted to ascertain the content of cholesterol, pigments and calcium salts. We report the results of our study and the conclusions we have drawn.

Patients and methods

Thirty-eight patients undergoing surgery for gallstones were examined. Eight patients who underwent gastrectomy and had normal liver laboratory tests and normal gallbladders served as controls. The stones and bile obtained during the operation were sent to the laboratory during or immediately after the operation. The gallstones were washed with saline and water, then air-dried at 37 °C overnight and ground in a mortar. The chemical analysis was then conducted according to the technique of Levy et al. (1976).

The fresh bile sample was analysed by the following micromethod: 2 ml of bile fluid were extracted directly with chloroform and, after centrifugation, a portion of this extract (0·2 ml) was used for the estimation of cholesterol by the Liebermann–Burchard reaction, as modified by Burke et al. (1974).

Since 90–95 per cent of bile salts are insoluble in chloroform, a portion of the remaining extracted bile (0·2 ml) was employed for the determination of total cholates, according to the procedure of Sutor et al. (1976). The total bile salts were obtained by assuming that the ratio of total cholate to bile salt remains relatively constant at 1 : 2·5 (Sjövall, 1960), and by taking into consideration the observations of Sutor et al. (1976) as to the variations in and the interpretation of such results.

The concentration of phospholipids was estimated in 0·1 ml of the non-extracted bile through digestion with sulphuric acid, oxidation with 30 per cent hydrogen peroxide and estimation of the phospholipid phosphorus using the method of Goodwin (1970).

By using standards expressed as mmol/l the absolute value of each component was obtained. These results were subsequently converted to percentage components and recorded on triangular coordinate graphs, according to the method of Admirand and Small (1968), for the determination of the solubility status of the main component—cholesterol. The osmolarity of the fresh bile samples was estimated with a Fiske osmometer, model G–66 (Fiske, Massachusetts, USA), operating by the principle of cryoscopy. The results were expressed as mmol/l of total components.

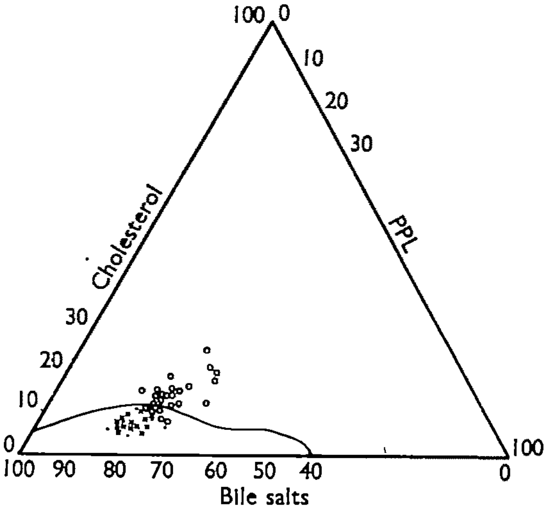

Fig. 1. Percentage composition of bile from 46 patients. ○, Patients with cholesterol stones ($n = 24$); ×, patients with pigment and pigment-mixed stones ($n = 14$); ●, control patients ($n = 8$). PPL, Phospholipid.

Results

The criterion for the definition of 'cholesterol stone' was that of Levy et al. (1976), who found a 60–100 per cent cholesterol content in 68 per cent of gallstones in Israel. Our results, for mean cholesterol content in gallstones, were similar to those reported by Sutor and Wooley (1971) in white Americans—76·2 per cent in women and 68·4 per cent in men. The classification of gallbladder stones according to this criterion is given in *Table I.* The respective bile analyses were arranged in the corresponding groups, and *Table II* shows the percentage composition of the three components for the two groups and the controls. *Fig.* 1 shows the results as expressed on triangular coordinates (Admirand and Small, 1968). This figure shows a 'supersaturation' of cholesterol in 19 of the 24 cases of bile containing cholesterol stones. The analyses of the bile from the 8 subjects in the control group and the 14 with pigment stones are inside the micellar zone (cholesterol 'undersaturation').

The osmolarity of the bile in the different groups is given in *Table III.* This shows that the osmolarity of

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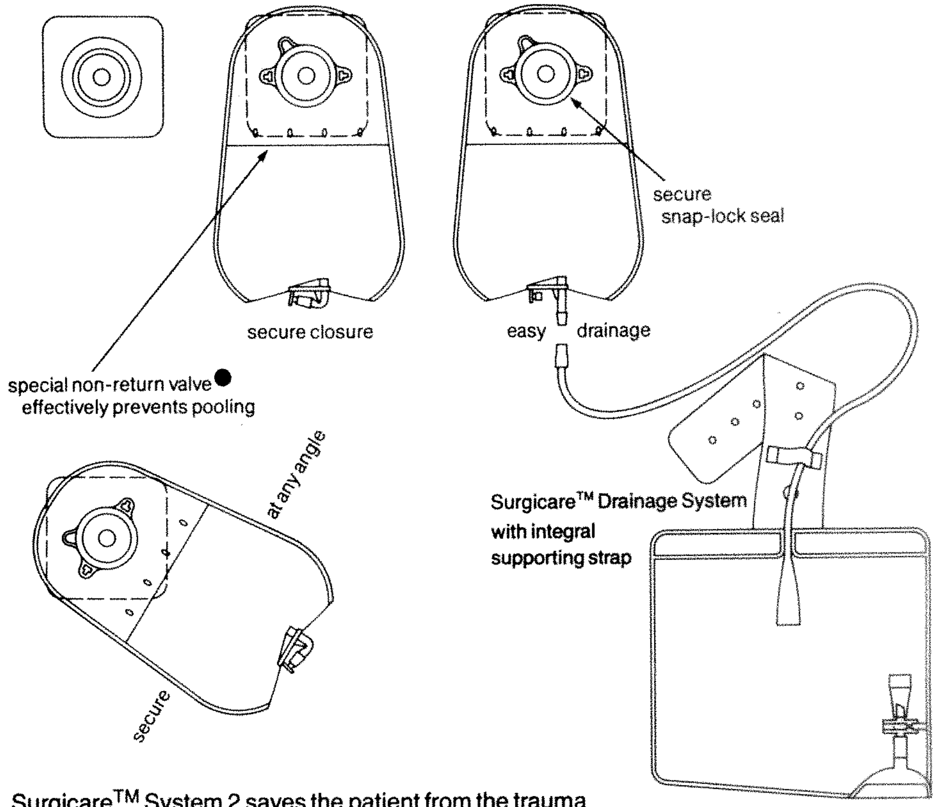

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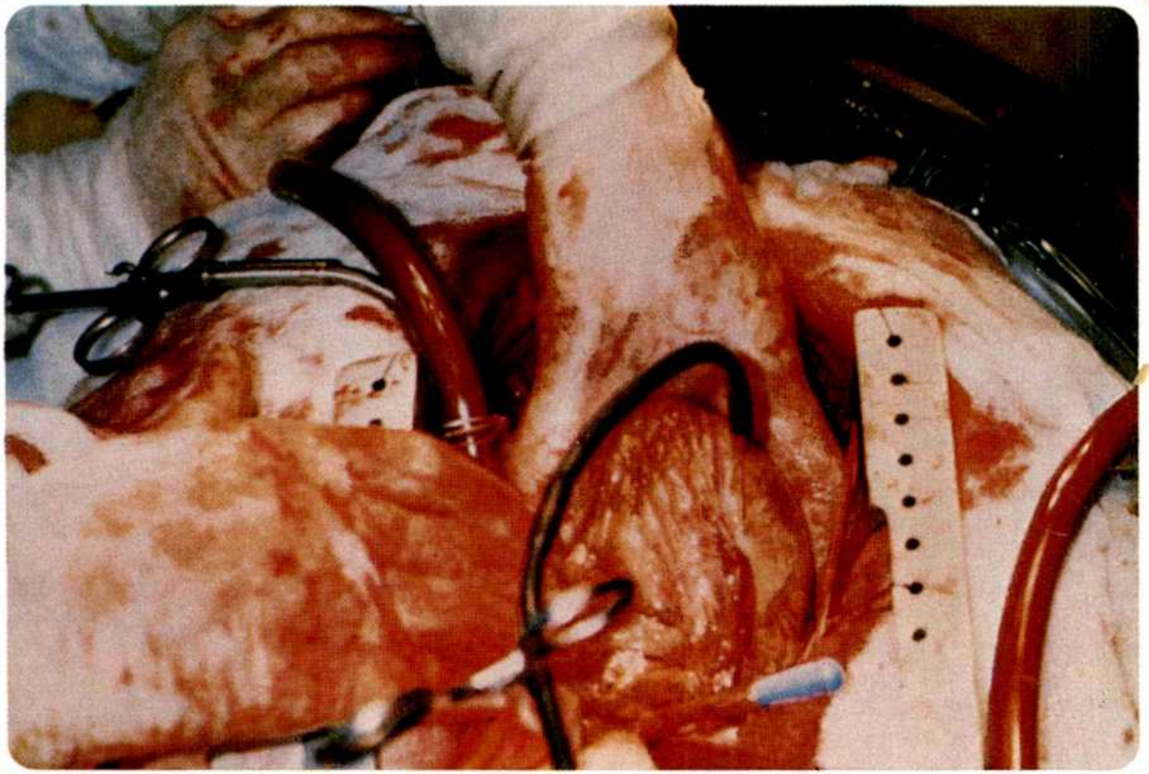

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1 Brit med J (1978), **1**, 1603
2 Thorax (1978), 33, **1**, 130
3 Brit med J (1978), **2**, 536
4 Brit med J (1970), **4**, 455
5 Zbl Bakt Hyg., I Abt Orig A (1976), **236**, 235

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Table I: GALLBLADDER STONE CLASSIFICATION

Group	No.	%	Composition of stones Cholesterol (%)	Pigment (%)	Calcium (%)
1. Cholesterol stones	24	63·2	60–100	< 30	< 10
(including pure cholesterol stones)	(6)	(15·8)			
2. Pigment stones or pigment-mixed stones	14	36·8	< 60	40–100	< 10
(including pure calcium stones)	(2)	(5·3)	< 20	< 30	30–100

Table II: PERCENTAGE COMPOSITION OF GALLBLADDER BILE

Group	Cholesterol Mean ±s.d.	Range	Bile salt Mean ±s.d.	Range	Phospholipids Mean ±s.d.	Range
1. Cholesterol stone forming bile ($n = 24$)	13·4 ±6·5	7–25	68·0 ±9·4	60–75	18·6 ±8·3	12–28
2. Pigment or pigment-mixed stone forming bile* ($n = 14$)	6·2 ±4·5	4–11	77·5 ±5·5	74–80	16·3 ±6·5	12–30
3. Controls ($n = 8$)	6·6 ±4·5	5–11	76·4 ±8·0	70–84	17·0 ±7·0	11–28

* Pure calcium stones included.

Table III: BILE FLUID OSMOLARITY

Group	Bile fluid osmolarity (mosmol/l) Mean±s.d.	Range
Cholesterol stones ($n = 24$)	318±29	274-376
Pigment-mixed stones ($n = 14$)	351±40	286-440
Controls ($n = 8$)	304±20	262-330

bile in those with pigment stones was significantly higher than in either controls or those with cholesterol stones.

Discussion

Our results are in accordance with those found in the literature, which suggest that a 'supersaturation' of cholesterol is associated with the formation of cholesterol gallstones.

The osmolarity of the bile in those with pigment stones was significantly higher than in those with cholesterol stones or no stones. In 3 patients with pigment stones, the osmolarity was outside the scale of the osmometer; the determination was impossible, because the bile was so viscous and rich in mucus. In 2 of these cases the bile contained micro-organisms. These findings suggest that an 'overconcentration' of all bile components (i.e. pigments, calcium salts, proteins, mucus and cellular debris) is associated with the formation of pigment (pure or mixed) stones.

Our findings are in agreement with the views of Trotman et al. (1974), according to whom the formation of pigment stones involves the precipitation of bilirubin, bile salts and as yet unidentified material.

References

ADMIRAND W. H. and SMALL D. M. (1968) The physico-chemical basis of cholesterol gallstone formation in man. *J. Clin. Invest.* **47**, 1043–1052.

BELL G. D., DOWLING R. H., WHITNEY B. et al. (1975) The value of radiology in predicting gallstone type when selecting patients for medical treatment. *Gut* **16**, 359–364.

BURKE R. W., DIAMONDSTONE B. I., VELAPOLDI R. A. et al. (1974) Mechanisms of the Liebermann–Burchard and Zak color reactions for cholesterol. *Clin. Chem.* **20**, 774–782.

GILAT T., GELMAN-MALACHI E., STADLER J. et al. (1977) Bile composition in a Tel-Aviv population. *Isr. J. Med. Sci.* **13**, 320–323.

GOODWIN J. F. (1970) Quantification of serum inorganic phosphorus, phosphatase and urinary phosphate without preliminary treatment. *Clin. Chem.* **16**, 776–780.

LEVY N., GELMAN-MALACHI E., PELED Y. et al. (1976) Cholesterol content of gallstones in Israel. *Isr. J. Med. Sci.* **12**, 1331–1332.

SJÖVALL J. (1960) Bile acids in man under normal and pathological conditions. Bile acids and steroids. *Clin. Chim. Acta* **5**, 33–41.

SUTOR D. J., COWIE A. G. A. and CLARK C. G. (1976) Some observations on gallstones and bile composition. *Br. J. Surg.* **63**, 44–46.

SUTOR D. J. and WOOLEY S. E. (1971) A statistical survey of the composition of gallstones in eight countries. *Gut* **12**, 55–64.

TROTMAN B. W., OSTROW J. D. and SOLOWAY R. D. (1974) Pigment vs. cholesterol cholelithiasis: comparison of stone and bile composition. *Am. J. Dig. Dis.* **19**, 585–590.

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Does obstructive jaundice adversely affect wound healing?*

M. G. GREANEY, R. VAN NOORT, A. SMYTHE AND
T. T. IRVIN†

SUMMARY
The effect of obstructive jaundice on wound healing has been investigated in an experimental study of abdominal wounds in rats following ligation and division of the common bile duct. Animals were jaundiced for 2 weeks before a second operation at which the abdominal wounds were made. The wounds in jaundiced and control animals showed no significant differences in mechanical strength during a 21-day period of study but there was a significant delay in the accumulation of collagen in the wounds of jaundiced animals. The findings suggest that the biochemical changes in the wounds of jaundiced animals did not interfere with wound repair and cast doubt on the thesis that jaundice has an adverse effect on wound healing.

It has been shown that jaundiced patients have an increased incidence of abdominal wound dehiscence and incisional hernia (Ellis and Heddle, 1977). However, a recent clinical study has suggested that impaired wound healing in jaundiced patients is not caused by the jaundice or the associated metabolic disturbance (Irvin et al., 1978). Jaundiced patients may have several other abnormalities which affect wound healing and, in an attempt to determine the effect of jaundice on wound repair, we have studied abdominal wound healing in rats following ligation and division of the common bile duct.

Material and methods

Male Wistar rats weighing 240–280 g were used throughout the study, which was conducted in three parts.

1. Effect of ligation and division of the common bile duct

In this part of the study 55 animals were used. Under open ether anaesthesia, using a clean operating technique, the common bile duct of the rat was exposed through a right subcostal incision and divided between 5/0 silk ligatures, as described by Lee (1972). The subcostal wound was closed with 2/0 Dexon.

Five animals were sacrificed for basal biochemical and haematological investigations of blood taken by cardiac puncture and further groups of 5 animals were sacrificed weekly for 5 weeks. Haemoglobin, prothrombin time, total bilirubin, total protein, albumen, alkaline phosphatase and SGPT were estimated.

2. Estimation of mechanical strength of abdominal wounds

A new techique of testing the mechanical strength of abdominal wounds *in vitro* was used in this study. This technique was based on the measurement of mechanical stress occurring at the time of rupture (σ) of a diaphragm of abdominal musculature distended by water.

In such a system the stress developed is defined by the formula $\sigma = Pr/2t$ (Cottrell, 1964), where P is the pressure applied, r is the radius of the curvature and t is the thickness of the membrane at failure (*Fig.* 1). Therefore, when r and t are calculated for a known value of P, the membrane (rupture) stress, σ, can be determined. Details of the calculation of r and t have been published previously (Van Noort et al., 1978).

One hundred and ninety-two rats were used in this part of the study, divided into two groups of 96 animals each. Animals

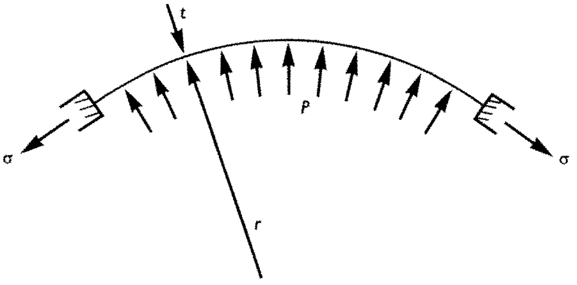

Fig. 1. The principle of the diaphragm method of testing. The stress (σ) developed in the distended membrane.

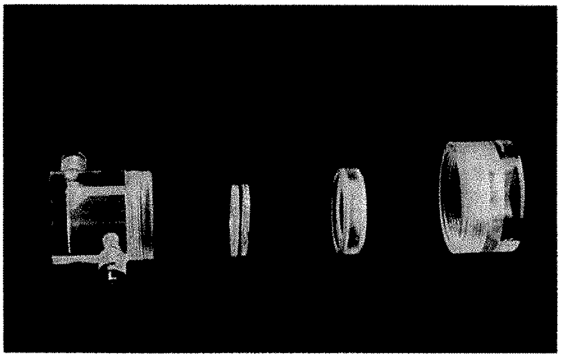

Fig. 2. Exploded view of the Perspex diaphragm testing chamber.

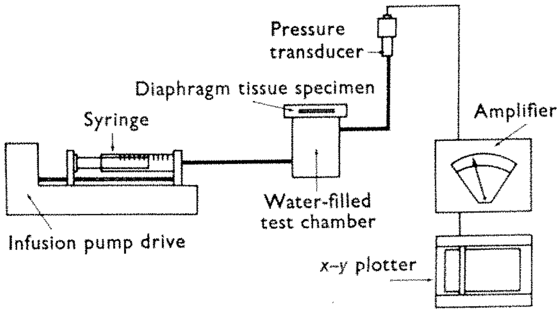

Fig. 3. Diagram of the apparatus for mechanical strength measurements.

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* Based on a communication to the Surgical Research Society, January 1978.

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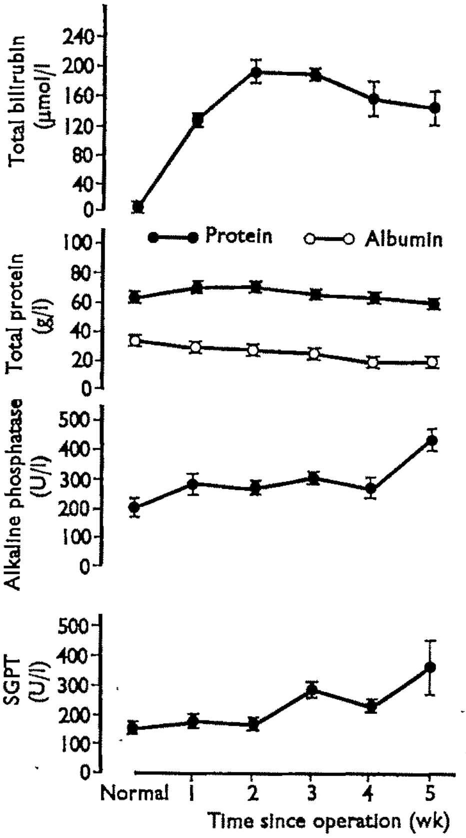

Fig. 4. The biochemical changes in jaundiced rats (mean ± s.e. mean).

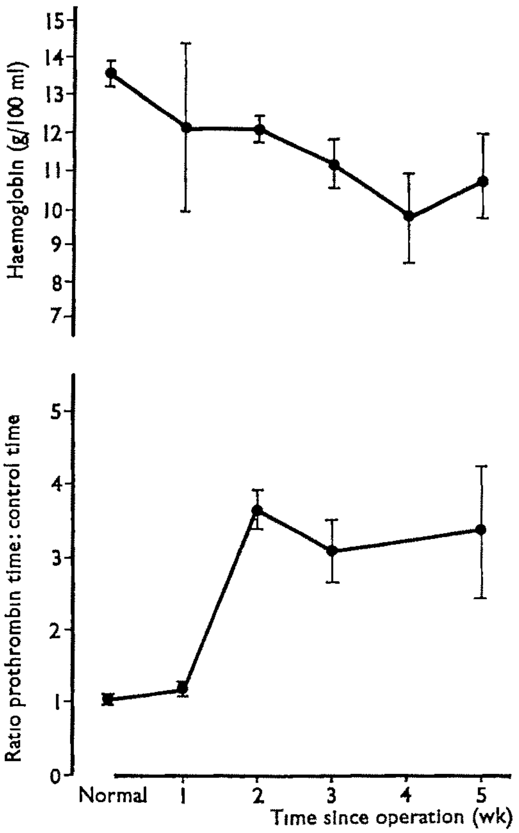

Fig. 5. The haematological changes in jaundiced rats (mean ±s.e. mean).

from one of the groups underwent ligation and division of the common bile duct and the other animals had a sham procedure, without division, and acted as a control group. The rats were anaesthetized again 2 weeks later and a 1-cm incision made in the left side of the abdominal wall. The abdominal muscle was closed as a layer with continuous 3/0 silk and the skin closed as a separate layer.

Jaundiced and control animals were sacrificed in groups of 12 at 1, 3, 5, 7, 9, 11, 14 and 21 days after the operation by overexposure to ether. After sacrifice the skin of the abdominal wall was carefully dissected from the muscular layer and the latter was carefully removed from the animal. Using a specially designed punch, two diaphragms, 30 mm in diameter, were excised from the abdominal muscle. One diaphragm was removed from the unwounded right side of the abdominal wall and the other, with the 1-cm wound at its centre, was removed from the left side. The thickness of the tissue was measured with a dial gauge micrometer.

Both diaphragms were mounted and tested for each animal. The wounds were tested with sutures *in situ* to avoid damage to the tissue. With the sutures *in situ* failure of the wounds occurred between sutures; the sutures therefore do not have a strengthening effect on the abdominal wounds.

The diaphragm tissue was mounted between Perspex rings with an internal diameter of 20 mm using a cyanoacrylic cement. The assembly was then introduced into a Perspex testing chamber and screwed into position (*Fig.* 2). The test chamber was filled with water and pressurized at a constant rate by an infusion pump (Harvard model 900). Distension of the diaphragm of tissue ultimately resulted in the bursting failure of the tissue. The pressure developed in the test chamber was measured with a pressure transducer (AB model 2000 A3) and recorded on an x–y plotter for a permanent record of the pressure-volume curve (*Fig.* 3). The pressure and volume at failure and the original thickness of the tissue were fed into a computer (Data General Nova 320) and the rupture stress for wounded and unwounded tissue (σw and σuw) computed. Measurements of rupture stress of wounded and unwounded tissue from each animal enabled the ratio of the two ($\sigma w/\sigma uw$) to be calculated. The value ($R\sigma$) disposes of variations between individual animals and approaches unity as healing progresses.

3. Estimation of the collagen accumulating in the abdominal wall wounds

One hundred and twelve rats were used in this part of the study. Seventy-two animals underwent ligation and division of the common bile duct and 40 had sham procedures Animals in both groups had 1-cm incisions made in the left side of the abdominal wall at a second operation 2 weeks later. The jaundiced animals were in groups of 9 and the controls in groups of 5. Groups were sacrificed at 1, 3, 5, 7, 9, 11, 14 and 21 days after the second operation.

After sacrifice the muscular abdominal wall was dissected from the animals and, using a special template cutter, a specimen of the wound measuring 1×0·5 cm was excised. This ensured that all samples were of standard size (Irvin, 1974).

Specimens were analysed by estimating the sample collagen values of the tissue using a variation of the method described by Prockop and Udenfriend (1960). Sample collagen was estimated rather than collagen concentration because of possible errors in using the latter value because of oedema and serum proteins in the healing wounds (Woessner, 1968).

Statistical analysis

Wilcoxon's rank sum test was used for the statistical analysis of the effects of ligation and division of the common bile duct (experiment 1). The Student *t* test was used in experiments 2 and 3.

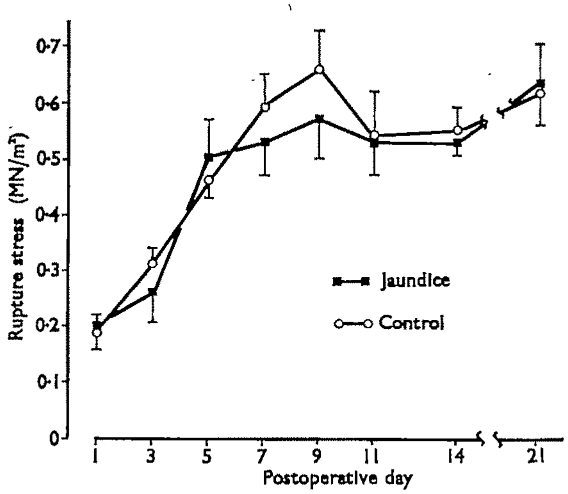

Fig. 6. Rupture stress (MN/m^2) values of abdominal wounds, jaundiced and control animals (mean ±s.e. mean).

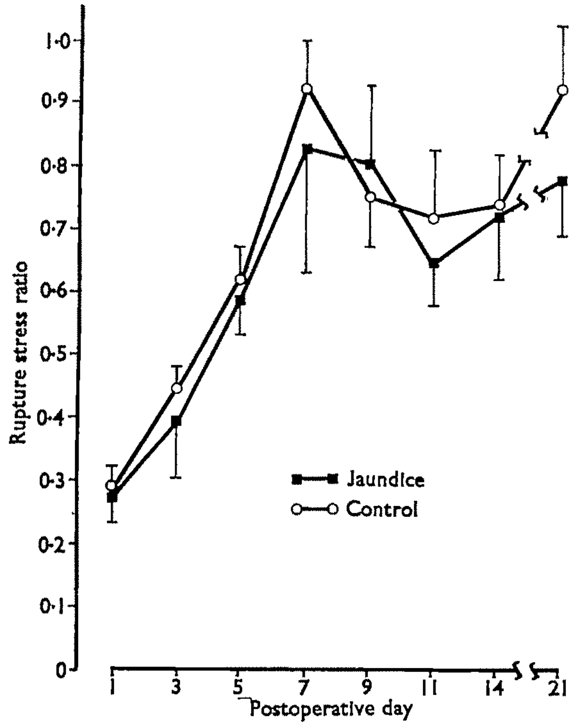

Fig. 7. Rupture stress ratio values of abdominal wounds, jaundiced and control animals (mean ± s.e. mean).

Results

1. *Effect of ligation and division of the common bile duct*

Biochemical estimations: All animals were obviously jaundiced within a few days of the operation and the values of total bilirubin, total protein, albumen, alkaline phosphatase and SGPT are shown in *Fig*. 4. The increase in total bilirubin is significant at 1 week after operation ($P<0{\cdot}001$). In the jaundiced animals there was a significant decrease in serum albumin 2 weeks after operation ($P<0{\cdot}01$).

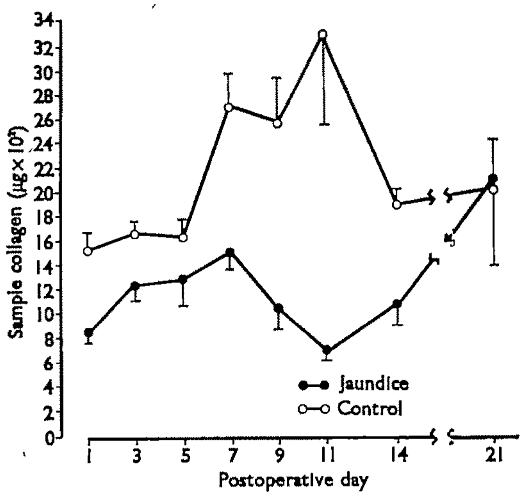

Fig. 8. Sample collagen measurements (mg) of abdominal wounds, jaundiced and control animals (mean ±s.e. mean).

Haematological estimations: *Fig*. 5 shows that there was a fall in the haemoglobin levels in the rats which became significant at 3 weeks after operation ($P<0{\cdot}05$). There was a dramatic rise in the prothrombin time in animals jaundiced for more than 1 week. Unfortunately no prothrombin times were measured in animals jaundiced for 4 weeks because of clotting of samples in the heparinized tubes.

2. *Estimation of mechanical strength of abdominal wounds*

Seventy-three jaundiced animals were available for testing and 86 of the sham control group. Each animal acted as its own control in the measurement of the rupture stress of the abdominal wall. In both groups there was an increase in rupture stress values to the ninth postoperative day and then a plateau (*Fig*. 6). Rupture stress ratio measurements followed a similar trend but peaked earlier, at 7 days (*Fig*. 7). There were no significant differences between measurements of rupture stress of wounded tissue and the rupture stress ratio for the jaundiced or control animals, up to and including the twenty-first postoperative day.

3. *Estimation of the collagen accumulating in the abdominal wall wounds*

Nine of the jaundiced and one of the control animals died in this part of the study, leaving 63 and 39 animals respectively for sacrifice. Sample collagen measurements in the abdominal wounds in jaundiced and control animals are presented in *Fig*. 8. Values in the control animals were significantly higher than in jaundiced rats (with the exception of the fifth postoperative day) until day 21 ($P<0{\cdot}01$). The collagen content of the abdominal wounds in control animals increased gradually until the eleventh day and then fell on the fourteenth and twenty-first days. Abdominal wound collagen in jaundiced animals behaved differently: there was an initial rise until 7 days, a reduction after 11 days and a second rise until 21 days when the values were similar to those of control animals.

Discussion

The evaluation of the effect of jaundice, or any other factor, on wound healing in man is complicated by the presence of other factors in the patient (Ellis, 1977). The jaundiced patient may, for example, have malignant disease or be malnourished. To isolate the factor under investigation it is necessary to undertake animal studies. Bayer and Ellis (1976) have done this in a study of the effects of obstructive jaundice on wound healing in jaundiced rats.

In contrast to the report of these workers, however, in a study in the same animal species and using a similar technique, we have found that ligation and division of the common bile duct not only produced jaundice but also a significant derangement of hepatic metabolism, with anaemia and hypoalbumenaemia. These findings are comparable with those of Than Than (1976) from her animal study.

This experimental study has demonstrated that mechanical strength measurements of abdominal wounds did not show any difference from similar wounds in anicteric control animals. There was some evidence of biochemical disturbance in the healing wounds of the jaundiced animals because collagen accumulated more slowly in the wounds of jaundiced animals.

In their experimental study, Bayer and Ellis (1976) showed that the bursting pressure of abdominal wounds was reduced in jaundiced rats 4 days after operation. However, the wounds in the stomachs of these animals were no weaker than those in controls, although in their histological and angiographic studies the healing process was seen to be delayed in the stomach incisions and in parietal peritoneal defects.

Than Than (1976) showed in radioisotope studies that prolyl hydroxylase activity was reduced in skin wounds of jaundiced rats. This enzyme catalyses one of the rate-limiting stages in the synthesis of collagen. However, in a parallel study she was unable to show any significant difference in tensile strength between skin wounds in jaundiced and comparable control animals.

The studies of Lee (1972) showed that migration of reticuloendothelial cells and fibroblasts into experimental granulomata was delayed in jaundiced animals. Lee concluded from this study that this represented a deficiency in the collagen components of wound healing.

The findings of previous studies show some agreement with the present work in so far as they suggest that collagen metabolism is affected in jaundiced animals. However, there is less agreement with mechanical strength measurements. The discrepancy in mechanical strength measurements may be a reflection of the different techniques of measurement. The lack of standardization and confusing nomenclature have encouraged us to develop a new technique of mechanical testing of wounds in small animals based on the distension of a diaphragm of tissue. We consider that this technique more closely simulates the physiological conditions affecting the healing abdominal wound. Only the muscle layer of the abdominal wall was tested and this is the vital layer in the early stages of healing, the skin is elastic and of little supporting value (Douglas, 1952).

The significance of the changes in collagen metabolism in the jaundiced animals is uncertain. They may be related to other hepatic disturbances, especially hypoproteinaemia, rather than any effect of jaundice alone.

Our recent clinical study (Irvin et al., 1978) also casts doubt on the significance of jaundice in wound healing. The incidence of wound failure, dehiscence and incisional hernia was increased only in those patients whose jaundice was a result of malignant disease. Therefore, it appears that other factors may be responsible for defective wound repair in jaundiced patients.

Acknowledgements

We are pleased to acknowledge the assistance of the Department of Chemical Pathology, the Children's Hospital, Sheffield, and the Department of Haematology, the Royal Infirmary, Sheffield, in performing the biochemical and haematological investigations for the study.

References

BAYER I. and ELLIS H. (1976) Jaundice and wound healing: an experimental study. *Br. J. Surg.* **63**, 392–396.

COTTRELL A. H. (1964) In: *The Mechanical Properties of Matter.* New York, Wiley, p. 122.

DOUGLAS D. M. (1952) The healing of aponeurotic incisions. *Br. J. Surg.* **40**, 79–84.

ELLIS H. (1977) Wound healing. *Ann. R. Coll. Surg. Engl.* **59**, 382–387.

ELLIS H. and HEDDLE R. (1977) Does the peritoneum need to be closed at laparotomy? *Br. J. Surg.* **64**, 733–736.

IRVIN T. T. (1974) Factors affecting the healing of colonic anastomoses. ChM Thesis, University of Aberdeen.

IRVIN T. T., VASSILAKIS J. S., CHATTOPADHYAY D. K. et al. (1978) Abdominal wound healing in jaundiced patients. *Br. J. Surg.* **65**, 521–522.

LEE E. C. G. (1972) The effect of obstructive jaundice on the migration of reticuloendothelial cells and fibroblasts into early experimental granulomata. *Br. J. Surg.* **59**, 875–877.

PROCKOP D. J. and UDENFRIEND S. (1960) A specific method for the analysis of hydroxyproline in tissues and urine. *Analyt. Biochem.* **1**, 228–239.

THAN THAN (1976) Skin prolyl hydroxylase and tensiometry in jaundice. PhD Thesis, University of Glasgow.

VAN NOORT R., GREANEY M. G., BLACK M. M. et al. (1978) A new *in vitro* method for the measurement of mechanical strength of abdominal wounds in laboratory animals. *Engineering in Medicine* 7, 217–221.

WOESSNER J. F. JUN. (1968) In: GOULD B. S. (ed.) *Treatise in Collagen*, 2. London, Academic Press.

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The surgical treatment of axillary hyperhidrosis

LEIF BERGKVIST AND LENNART ENGEVIK*

SUMMARY

Axillary hyperhidrosis is a common condition and young people often suffer unnecessarily for many years in spite of the availability of good surgical methods for cure. We describe our own modification of Pettersson and Strömbäck's (1970) method of excision of the sweat glands. During the years 1972–6 218 axillary operations have been performed on 109 patients at the surgical clinic in Västerås for axillary hyperhidrosis. We reviewed 104 of these and found that 71 patients were completely satisfied and only 7 unsatisfied. Twelve patients wanted to be reoperated either because they still sweated or because they were unhappy with their scars. Thus, we found that overall the surgical methods are safe, simple and give good results.

AXILLARY hyperhidrosis is a common condition. Patients often suffer for many years without receiving adequate treatment. These patients are continually wet under the arms and the sweat often penetrates the outer clothing. As a result of the sweating, local skin changes occur such as eczema and candidiasis. Bacterial activity causes an odour that is embarrassing for the patient and people nearby. The embarrassment may further increase the sweating tendency. The symptoms associated with hyperhidrosis often first appear at puberty and may result in social isolation.

Anatomy and physiology

The sweat glands in the axilla are of two types, the apocrine and the eccrine glands (Frewin and Downey, 1976). The apocrine glands are found in connection with hair follicles, not only in the axilla but also in the perineum and areolar tissue of the breast. They excrete a milky, odourless fluid, that may be broken down by bacteria into pungent fatty acids. These glands are innervated by the adrenergic fibres of the sympathetic nervous system, and increase their production in response to stress.

The eccrine glands are found throughout the skin and excrete a clear, odourless, salty fluid. They are innervated principally by cholinergic fibres from the thoracolumbar sympathetic nervous system, but have some connection with the adrenergic fibres and are influenced by stress.

It is not clear which type of gland is responsible for the main production of sweat in patients with hyperhidrosis. Rindal and Eskeland (1976) have found an increase of the apocrine glands in patients with hyperhidrosis, while other investigators such as Rigg (1977) doubt whether these glands alone are responsible for the overproduction of sweat. In the majority of cases the aetiology is not known and the histological appearance of the sweat glands is normal (Monro et al., 1974).

Treatment

The medical treatment of hyperhidrosis gives bad results. Anticholinergic drugs have some effect but usually such a high dosage is needed that side-effects become intolerable. The numerous commercial deodorants available have no effect in hyperhidrosis. Shelley and Hurley (1975) describe the use of approximately fifty aluminium salts plus salts of sirconium, zinc, bismuth, copper, magnesium and mercury. They have also listed a number of organic compounds to reduce sweating, including anticholinergic agents, different types of acids, aldehydes and quarternary ammonium compounds. However, Scholes et al. (1978) report good results with 20 per cent aluminium chloride hexahydrate in absolute alcohol. Local radiation has been used but this can give rise to permanent skin damage.

Sympathectomy for hyperhidrosis has been described by Rask and Stefansson (1973), Ellis (1975) and Keaveny et al. (1977). However, as a result of the high complication rate, the operation is rarely used. Different methods that aim to reduce the total mass of glandular tissue have been described. Skoog and Thyresson (1962) described a method of undermining four skinflaps and excising the enlarged sweat glands on the underside. Pettersson and Strömbäck (1970) described a method (*Fig.* 1*a*) with central excision and trimming of the edges. In 1973 Bretteville-Jenssen described an excision method using a Z-flap and Eldh and Fogdestam (1976) described another excision method where the scar was either M- or V-shaped. In 1975 Jemec described a glandular curettage through a small incision. Recently we have adopted a further modification of this method (*Fig.* 1*b*), which has certain benefits when compared with the earlier method of Pettersson and Strömbäck (1970).

Method

The patient lies supine with the arms abducted to approximately 110°. The hairline is marked (*Fig.* 1*b*) and an oval of hair-bearing skin is excised in the inferior part of the hair-carrying area. The superior flap is undermined and the glands excised from its underside. The wound is closed with sutures that include the underlying fascia.

Patients

Between 1972 and 1976 218 axillary operations for axillary hyperhidrosis have been performed on 109 patients. All patients were given a questionnaire and 104 responded (95·4 per cent); 28 were men and 76 women. The average age was 31·5 years and the age range is shown in *Table I*. The average duration of symptoms was 14·2 years, but 5 patients have had symptoms for more than 30 years. The youngest patient in the series, a girl of 15, had had symptoms for only 1½ years (*Table II*). *Table III* lists the presenting problems. All had sweating and the majority also had penetration through their outer clothing. An unpleasant body odour worried 56·6 per cent, whereas 67 per cent found that people around them remarked on their excessive sweating and offered well-meaning advice on treatment. Thirty-one per cent had withdrawn from normal social life because of social and psychiatric problems. Before operation all patients had had some local treatment. All had tried diverse deodorants, 73 had tried some form of 'special' application for hyperhidrosis and 51 had taken some form of medicine, such as anticholinergic drugs or a sedative. No patient had good results from conservative medical treatment. All the patients were operated upon under general anaesthesia

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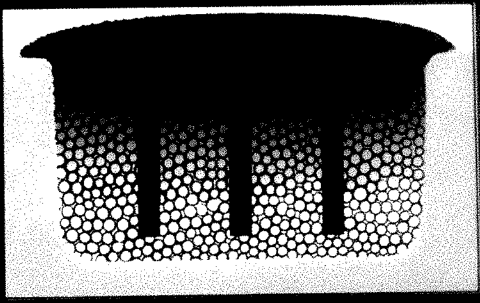

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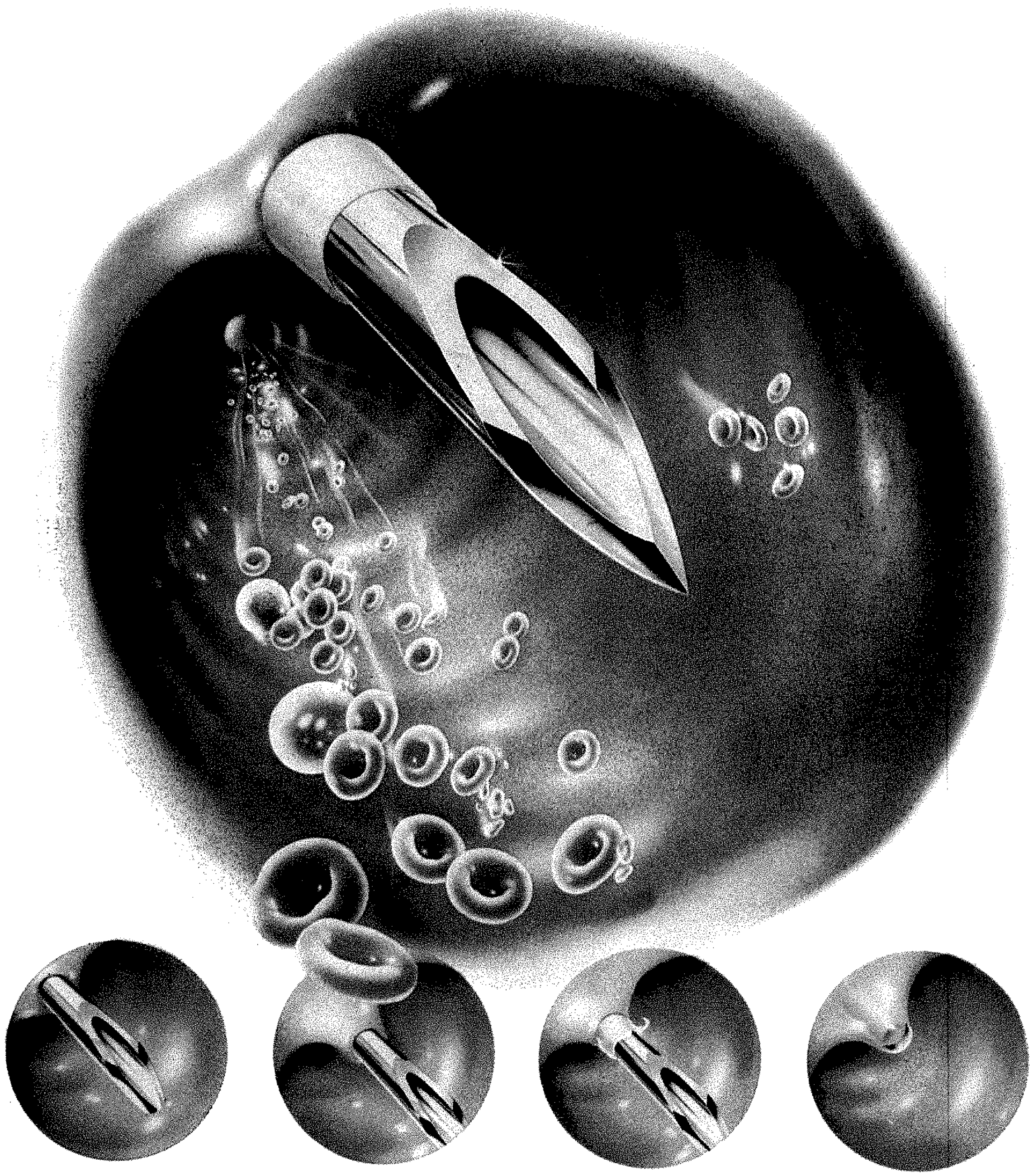

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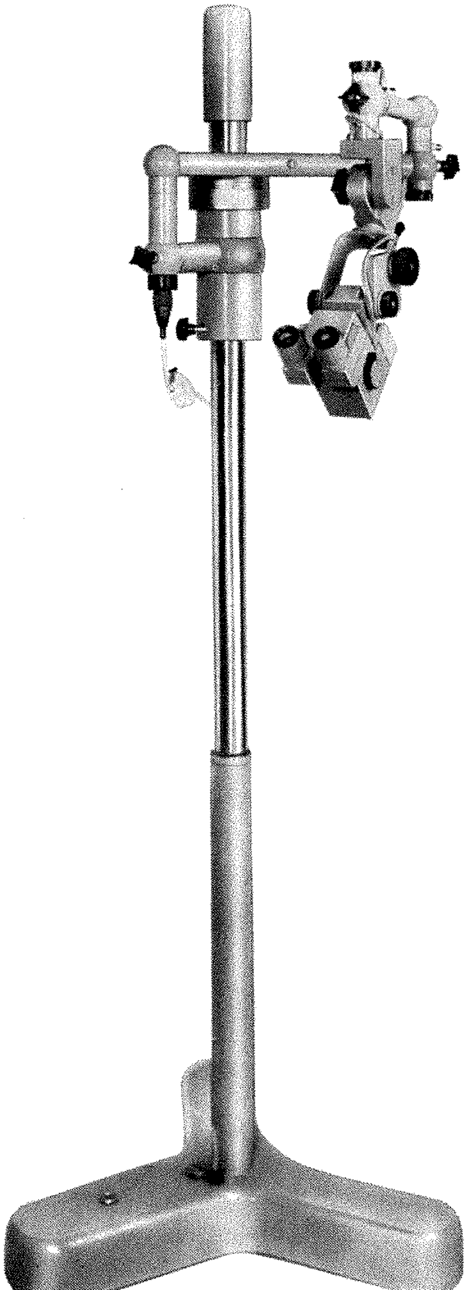

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Infant dosage Intralipid 10% or 20%: 15–20 ml per kg body weight in 24 hours.

Contra-indications, warnings, etc. Intralipid is contra-indicated in pathological hyperlipaemia and severe liver damage.

Precautions When daily intravenous fat administration for more than one week is indicated it must be ascertained, in order to prevent the development of cumulative lipaemia, that the patient is capable of eliminating the infused fat from the circulation, and this function can be tested in the following manner. In the morning following the first day's infusion, a citrated blood sample is drawn, preferably when the patient is still in a fasting state. The blood sample is centrifuged at 1 200–1,500 rpm. If the plasma is then strongly opalescent or milky, further infusion should be postponed. In the great majority of cases, plasma is completely clear 12 hours after the conclusion of an infusion of 2 g fat per kg body weight (corresponding to 20 ml of Intralipid 10% or 10 ml of Intralipid 20% per kg body weight). This test should be repeated at weekly intervals.

Pharmaceutical precautions Store at a temperature between 4°C and 8°C, and do not use after the date of expiry indicated. The contents of each bottle are for a single infusion and any residual emulsion should be discarded. No drugs should be added to Intralipid prior to or during infusion.

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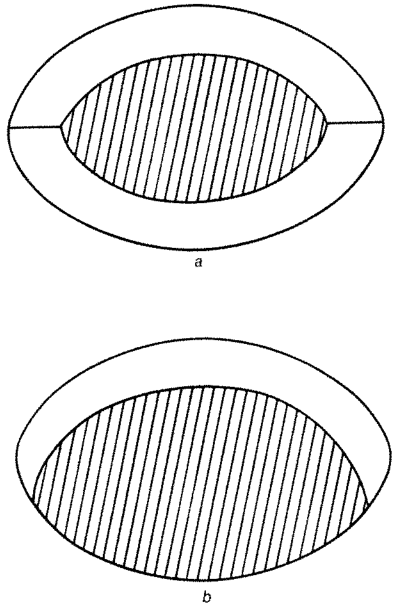

Fig. 1. *a*, The Pettersson–Strömbäck method. The outer line is the limitation of the hair-bearing area. The stretched area is excised and the white field undermined and sweat glands trimmed away. *b*, The authors' method. The inferior oval is excised and the upper flap is undermined. This method thus gives rise to only one skin flap and an interrupted scar line.

as inpatients. Skoog and Thyresson's (1962) four skin flap method was used in 11 patients and Pettersson and Strömbäck's (1970) method (*Fig.* 1*a*) in 93 patients.

Complications

Fifty-six patients have healed without complication, whilst 48 have had some postoperative problems, usually infection. We have classified as infected even those wounds with signs of inflammation around the sutures. It is worth noting that only one patient with infection required antibiotic therapy and that all infected wounds healed in 4–5 weeks. Minor skin necrosis occurred on four occasions and some patients developed cysts and seromas in the axilla that were treated by needle puncture and drainage.

Results

Nearly 70 per cent of the patients were completely satisfied with the operation. Of the other 33 patients (7 men and 26 women), 7 had only one-sided symptoms after the operation. One of these had just as much trouble as before the operation, while the remaining 6 were better but still not completely cured.

Of the 26 patients with bilateral problems, only 6 have as much trouble as before the operation. Seven patients did not experience any improvement after the operation. Thirteen patients (12 women) considered the scar to be cosmetically ugly but only 2 patients had diminished movement in the shoulder. Seven patients would not recommend the operation to a friend, though 2 of these belonged to the group that claimed to be completely satisfied. One of these would not recommend the operation beause of the ugly scar, whilst the other could not give any reason. Four patients found the operation unpleasant. Of the 'completely satisfied' patients, 17 still had some axillary sweating. Altogether 12 patients are to have another operation; some to try to diminish sweat secretion further and some to improve the scar. *Table IV* shows the symptom-free postoperative period for those patients whose sweating recurred. It is interesting to note that even among those patients who were failures there were only 2 who did not experience any diminished sweating; most were improved for a

Table I: AGE RANGE OF 104 PATIENTS OPERATED ON FOR AXILLARY HYPERHIDROSIS

Age (yr)	Male	Female	Total
<15	0	1	1
16–20	3	15	18
21–25	2	6	8
26–30	4	20	24
31–35	6	15	21
36–40	7	10	17
41–50	2	8	10
51–60	2	1	3
>60	2	0	2
Total	28	76	104

Table II: DURATION OF SYMPTOMS IN 104 PATIENTS OPERATED ON FOR AXILLARY HYPERHIDROSIS

Duration (yr)	Male	Female	Total
0–5	9	16	25
6–10	5	12	17
11–15	4	17	21
16–20	4	17	21
21–25	3	6	9
26–30	1	5	6
30	2	3	5

Table III: SYMPTOMS IN 104 PATIENTS OPERATED ON FOR AXILLARY HYPERHIDROSIS

Symptoms	Male	Female	Total	%
Sweating penetrating the outer clothing	28	76	104	100
Bad body odour	14	45	59	57
Social withdrawal	9	23	32	31
'Comments' from people in contact with the patient	15	55	70	67

Table IV: SYMPTOM-FREE PERIOD BETWEEN OPERATION AND RECURRENCE OF PROBLEMS

Months	Male	Female	Total
0	1	1	2
1	0	6	6
2	2	14	16
3	0	0	0
4	0	1	1
5	0	0	0
6	1	1	2
6–12	1	5	6
12	2	6	8

Table V: LENGTH OF SICKNESS BENEFIT PERIOD IN 104 PATIENTS OPERATED ON FOR AXILLARY HYPERHIDROSIS

Benefit period (wk)	Male	Female	Total
<1	2	4	6
1–2	10	22	32
2–3	6	21	27
3–4	4	18	22
4–5	4	6	10
>5	2	5	7

couple of months. Only 4 patients out of 11 patients operated on according to the four skin flap method were completely satisfied: 2 of these still sweated. Six of the 93 other patients were still bothered by severe arm sweat, one just as much as before the operation. One patient was not satisfied with the cosmetic result.

The average time off work for the whole series was 3 weeks for men and 3·2 weeks for women (*Table V*). Some patients went straight back to work after the operation, while in some cases concurrent illnesses extended the sickness benefit period.

Discussion

Hyperhidrosis is an embarrassing handicap. Medical treatment often fails, although Scholes et al. (1978) report good results with 20 per cent aluminium chloride hexahydrate in absolute alcohol if used continuously. There are several effective surgical techniques. These are of two fundamentally different types: first, the parenchyma reducing operation (Hurley and Shelley, 1963) and secondly, procedures that divide the efferent nerves. Sympathectomy is considered to be a difficult method liable to severe complications such as pneumothorax and Horner's syndrome (Keaveny et al., 1977). The procedures for reducing glandular parenchyma are easy to perform and are associated with no severe complications. In our material we found Pettersson and Strömbäck's (1970) method superior to Skoog and Thyresson's (1962) because the latter was technically more difficult and carried a greater risk of skin necrosis. Our own method has some advantages over that of Pettersson and Strömbäck in giving rise to only one skin flap, so reducing the dissection.

In our series of 104 patients approximately 70 per cent are completely satisfied, 20 per cent, though not quite satisfied, are so much better that they do not wish reoperation and 10 per cent are dissatisfied and need another operation. There were many minor infections but only 7 more severe complications, all of which healed without sequelae. We prefer general anaesthesia as we regard the risk of infection and skin necrosis to be greater with local anaesthesia. All patients were operated on as inpatients; they all preferred to go home the day after the operation although it would be possible for the operation to be performed on a day-care basis. In conclusion, we feel that patients with hyperhidrosis can be helped with an adequate, safe and proved surgical method of treatment. Thirty-three different surgeons all at different stages of their surgical training have operated upon the 104 patients in this series. No significant differences between the results could be found, however senior or junior the surgeon was.

References

BRETTEVILLE-JENSSEN G. (1973) Radical sweat gland ablation for axillary hyperhidrosis. *Br. J. Plast. Surg.* **26**, 158–162.

ELDH J. and FOGDESTAM I. (1976) Surgical treatment of hyperhidrosis axillae. *Scand. J. Plast. Reconstr. Surg.* **10**, 227–229.

ELLIS H. (1975) Hyperhidrosis and its surgical management. *Postgrad. Med.* **58**, 191–196.

FREWIN D. B. and DOWNEY J. A. (1976) Sweating—physiology and pathophysiology. *Aust. J. Derm.* **17**, 82–86.

HURLEY H. J. and SHELLEY W. B. (1963) A simple approach to the management of axillary hyperhidrosis. *JAMA* **186**, 109–112.

JEMEC B. (1975) Abrasio axillae in hyperhidrosis. *Scand. J. Plast. Reconstr. Surg.* **9**, 44–46.

KEAVENY T. V., FITZGERALD P. A. M., DONNELLY C. et al. (1977) Surgical management of hyperhidrosis. *Br. J. Surg.* **64**, 570–571.

MONRO D., VERBOV I., O'GORMAN D. J. et al. (1974) Axillary hyperhidrosis. *Br. J. Dermatol.* **90**, 325–329.

PETTERSSON L.-O. and STRÖMBÄCK J. O. (1970) Kirurgisk behandling av hyperhidros. *Sven. Läkartidningen* **67**, 5676–5680.

RASK B. E. and STEFANSSON T. (1973) Sympatectomi ved hyperhidrose. *Ugeskr. Laeger.* **135**, 699–701.

RIGG B. M. (1977) Axillary hyperhidrosis. *Plast. Reconstr. Surg.* **59**, 334–342.

RINDAL R. and ESKELAND G. (1976) Kirurgisk behandling av aksillaer hyperhidrose. *Tidsskr. Nor. Laegefören.* **23**, 1207–1209.

SCHOLES K., CROW K., ELLIS J. et al. (1978) Axillary hyperhidrosis treated with alcohol solution of aluminium chloride hexahydrate. *Br. Med. J.* **2**, 84–85.

SHELLEY W. B. and HURLEY H. J. jun. (1975) Studies on topical antiperspirant control of axillary hyperhidrosis. *Acta Derm. Venereol. (Stockh.)* **55**, 251–260.

SKOOG T. and THYRESSON N. (1962) Hyperhidrosis of the axillae: a method of surgical treatment. *Acta Chir. Scand.* **124**, 531–538.

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Congenital chylothorax: report of unique case associated with 'H'-type tracheo-oesophageal fistula

J. G. HARVEY, W. HOULSBY, K. SHERMAN AND M. H. GOUGH*

SUMMARY

A case of congenital chylothorax associated with a congenital 'H'-type tracheo-oesophageal fistula is reported. The development of the thoracic duct is described and the possible embryological association with tracheo-oesophageal fistula is discussed. The management of the case is reviewed.

THE first case of neonatal chylothorax was described by Stewart and Linner in 1926, although the condition in adults has been known since 1633 (Bower, 1964). Congenital 'H'-type tracheo-oesophageal fistula, first described by Lamb in 1873 (Ferguson, 1951), is a rare anomaly occurring in 1·8 per cent of all cases of tracheo-oesophageal fistula (Waterston et al., 1962). The association in a single patient is, we believe, unique.

Case report

J. W., a 2·95-kg girl, was delivered by forceps at 38 weeks, subsequent to a pregnancy complicated by hydramnios and pre-eclamptic toxaemia. During the first hour after birth the baby became progressively dyspnoeic and cyanosed with evidence of increasing peripheral circulatory failure. A chest radiograph revealed the presence of a large left pleural effusion (*Fig.* 1). Aspiration of 120 ml of yellow fluid and the insertion of an intercostal drain resulted in rapid improvement. Analysis of the fluid (*Tables I* and *II*) suggested the diagnosis of congenital chylothorax. The diagnosis was confirmed by injecting Patent Blue dye into the web space of the foot and observing the appearance of the dye in the chest drain 3 min after injection.

Lymphangiography was performed through a lymphatic on the dorsum of the foot and revealed normal limb, pelvic and abdominal lymph vessels and glands. A pool of contrast material was visible in the left superior mediastinum 1 h following the commencement of injection (*Fig.* 2). In the first 24 h of life, drainage of fluid by the intercostal catheter amounted to 280 ml. Subsequent drainage continued at a rate of 120–300 ml/24 h for 26 days, amounting to a total of 7·6 litres. Oral feeding was withheld to minimize chyle production and daily fluid requirements were administered intravenously. The volume of chyle lost was initially replaced volume for volume with plasma. On day 10, in the face of continuing chyle loss, parenteral nutrition was instituted and maintained throughout the period of leakage. Spontaneous closure of the fistula was encouraged by the use of a Gregory box to raise the end-expiratory intrapleural pressure to 10 cm of water. Drainage of the fluid was accomplished by means of free drainage through the intercostal drain until day 16 when the drain blocked. Following this, thoracentesis was performed daily until day 26 when a traumatic haemothorax was inadvertently produced, after which the chylous leak spontaneously ceased.

Following the introduction of oral feeding, the baby was noted to have difficulty with feeds, with choking, transient apnoeic attacks and intermittent abdominal distension when coughing. A diagnosis of 'H'-type tracheo-oesophageal fistula was entertained. Cine barium swallow was performed and showed no abnormality. The fistula was successfully demonstrated at bronchoscopy and oesophagoscopy. Operation was performed on day 76 of life. A left supraclavicular approach was used and this demonstrated a fistula at the level of the first

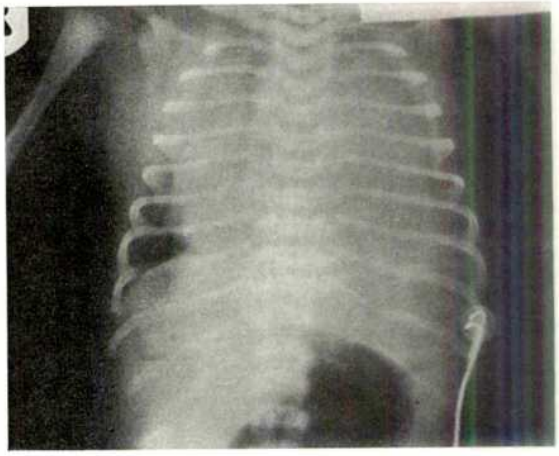

Fig. 1. Chest radiograph 4 h after birth showing left pleural effusion.

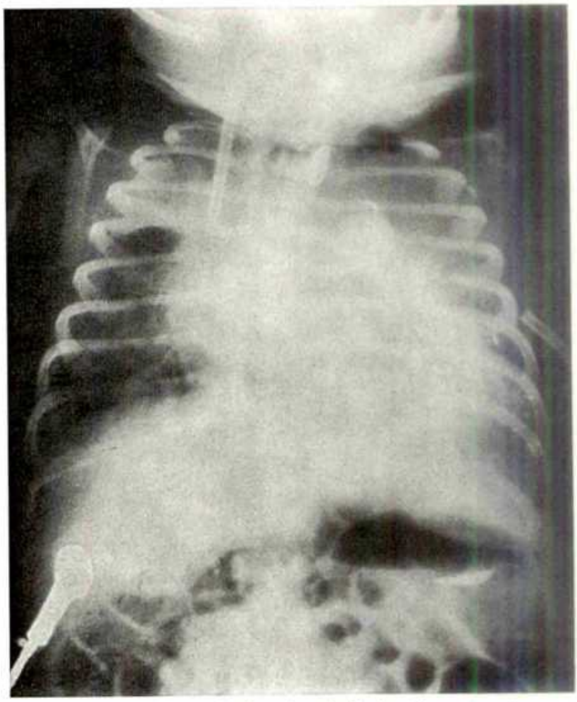

Fig. 2. Chest radiograph showing the leak of lymphangiographic contrast material into the left superior mediastinum and left pleural cavity.

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Table I: ANALYSIS OF CHYLE

Chyle	12 Jan. 1977	13 Jan. 1977–2 Feb. 1977	Total
Volume (ml/24 h)	450	250–300	7·6 l
Protein (g/dl)	3·3	—	—
WBC × 10^6/l	1250	—	—
Lymphocytes × 10^6/l	1062	—	—

Table II: ANALYSIS OF PLASMA

Plasma	12 Jan. 1977	21 Jan. 1977	2 Feb. 1977
Haemoglobin (g/dl)	15	11·1	9·2
WBC × 10^9/l	6·1	8·7	12·1
Lymphocytes × 10^9/l	1·09 (18%)	1·66 (20%)	4·2 (35%)
Protein (g/dl)	53·5	59·5	54

thoracic vertebral body. The fistula was ligated and divided. The child made an uncomplicated recovery and when she was seen at 12 months in the outpatient department, she was found to be gaining weight and developing normally. She has had no difficulty with feeding and her chest is now clinically and radiologically normal.

Discussion

Embryological aspects

The formation of the lymphatic system commences at about the 6th week of fetal life as outgrowths of venous endothelium (Sabin, 1902). The thoracic duct is formed by the fusion of caudal outgrowths from the jugular lymph sacs with cranial outgrowths from the cysterna chyli to form a single duct, although the persistence of multiple channels is not uncommon (Van Pernis, 1949).

Lymphaticopleura fistula resulting in chylothorax has been reported in association with a lymphangiomatous malformation of the thoracic duct (Rienhoff et al., 1964). Randolph and Gross (1957) suggested that a congenital abnormality of the duct may predispose to traumatic rupture at the time of delivery.

The separation of the trachea from the foregut should be complete by the 8th week. Any persistent communication presents as a form of laryngeal fissure or as a tracheo-oesophageal fistula usually associated with oesophageal atresia.

Local vascular accidents may arrest the differentiation and development of fetal tissues, and the coexistence of a lymphovascular abnormality and a tracheo-oesophageal fistula at the same somitic level in this infant suggests that some such factor was operative at the 6th to 8th week of fetal life.

Aspects of management

The rarity of congenital chylothorax has resulted in the slow evolution of satisfactory management. Although the 25 per cent mortality (Chernick and Reed, 1970) is probably due to extended conservative management in the absence of adequate nutrition, the incidence of spontaneous resolution in 50 per cent of cases (Randolph and Gross, 1957) and the difficulty of localization of the defect at operation make a trial of conservative therapy worth while. Management should be aimed at the early institution of satisfactory thoracic drainage either by intercostal tube or by repeated thoracentesis. Decancq (1965) suggested that continuous suction should be applied to the intercostal drain in order to promote re-expansion of the lung and to tamponade the visceral pleura against the defect; however, Randolph and Gross (1957) suggested that the use of suction is unwise since the maintenance of a low intrathoracic pressure will tend to keep the duct open and maintain the flow through the fistula.

An attempt was made on our patient to induce spontaneous closure by the use of a Gregory box to raise the end-expiratory intrapleural pressure to 10 cm of water (7·8 mmHg). Experimental work in sheep which demonstrated a mean pressure of 3–5 mm of mercury in the thoracic duct (Hall et al., 1965) would tend to justify this approach. The use of talc to promote pleurodesis at the site of the fistula is recommended by Gingell (1965) and in our case the occurrence of the haemothorax may well have had a similar effect.

The basal flow rate of lymph from the thoracic duct has been shown to be 1·38 ml kg^{-1} h^{-1} and this increases 10 times following a fatty meal (Bessone et al., 1971). Lesser increases in the rate of flow of lymph from the thoracic duct are brought about by protein and carbohydrate. Crandall et al. (1943) showed that in man the ingestion of water by mouth increased thoracic duct lymph flow. In view of these findings, steps should be taken to minimize the flow of chyle by withholding oral feeds or by substituting feeds of medium chain triglycerides which are absorbed directly into the portal system and do not increase the rate of flow of lymph from the thoracic duct (Frazer, 1943; Kosloske et al., 1974).

Total loss of protein in the chylous fistula in our patient amounted to 25 g over 26 days. Replacement of protein loss and the provision of adequate calories were accomplished by means of parenteral nutrition. Recent experience (Kosloske et al., 1974) has shown that this method of alimentation has several advantages over the traditional method of replacement of chyle intravenously (Forbes, 1944). Both lymphocyte depletion and haemorrhagic diatheses secondary to loss of clotting factors in chyle have been described (Brodman et al., 1974). In our case, despite a total loss of $6{\cdot}5 \times 10^6$ lymphocytes, no reduction in the peripheral circulating lymphocyte count was encountered. Coagulation studies showed no defect in clotting ability over the period of leakage. Current management should be directed to conservative therapy which should be maintained in the presence of good nutritional status and adequate ventilatory function for 3–4 weeks, since most fistulas close within this period (Randolph and Gross, 1957). Operative treatment is recommended if leakage continues after this or if there is deterioration of the patient's condition, despite parenteral feeding. Localization of the duct at operation is difficult. Hendy et al. (1962) recommend injection of an intravital dye into the lymphatic system to help localization of the duct. Surgical treatment should consist of suture ligation of the duct above and below the defect and direct suture of the mediastinal pleura.

Tracheo-oesophageal fistula without atresia ('H'-type fistula) in the neonate presents considerable diagnostic difficulty. The fistula is commonly present at the level of the first thoracic vertebra. Our infant demonstrated the triad of feeding difficulty with choking, periodic abdominal distension and recurrent respiratory tract infection, described by Waterston et al. (1962). Barium studies with bronchoscopy and oesophagoscopy should permit the demonstration of the defect in most cases (Sundal et al., 1975), but in some cases exploration on clinical evidence alone may be necessary. Direct ligation of the fistula is all that is required.

References

BESSONE L. N., FERGUSSON T. B. and BURFORD T. H. (1971) Chylothorax: collective review. *Ann. Thorac. Surg.* **12**, 527–550.

BOWER G. C. (1964) Chylothorax: observations in 20 cases. *Dis. Chest* **46**, 464–468.

BRODMAN R. F., ZAVELSON T. M. and SCHLIEBER G. L. (1974) Treatment of congenital chylothorax. *J. Pediatr.* **85**, 516–517.

CHERNIK N. and REED M. H. (1970) Pneumothorax and chylothorax in the neonatal period. *J. Pediatr.* **76**, 624–626.

CRANDALL L. A. jun., BARKER S. B. and GRAHAM D. G. (1943) Study of lymph flow from a patient with a thoracic duct fistula. *Gastroenterology* **1**, 1040–1048.

DECANCQ H. G. (1965) The treatment of chylothorax in children. *Surg. Gynecol. Obstet.* **121**, 509–512.

FERGUSON C. F. (1951) Congenital tracheo-oesophageal fistula not associated with atresia of the oesophagus. *Laryngoscope* **61**, 718–766.

FORBES G. B. (1944) Chylothorax in infancy. *J. Pediatr.* **25**, 191–200.

FRAZER A. C. (1943) Differentiation in the absorption of olive oil and oleic acid in the rat. *J. Physiol.* **102**, 306–312.

GINGELL J. C. (1965) Treatment of chylothorax by producing pleurodesis using iodised talc. *Thorax* **20**, 261–269.

HALL J. G., MORRIS B. and WOOLEY G. (1965) Intrinsic rhythmic propulsion of the lymph in the unanaesthetized sheep. *J. Physiol. (Lond.)* **180**, 336–349.

HENDY J. G., WALKER G. R. and DEGUZMAN V. C. (1962) Localization of the thoracic duct by peri-oesophageal injection of sky blue. *JAMA* **182**, 187–188.

KOSLOSKE A. M., MARTIN L. W. and SCHUBERT W. K. (1974) Management of chylothorax in children by thoracentesis and medium chain triglyceride feedings. *J Pediatr. Surg.* **9**, 365–371.

RANDOLPH J. G. and GROSS R. E. (1957) Congenital chylothorax. *Arch. Surg.* **74**, 405–419.

RIENHOFF W. F., SHELLEY W. M. and CORNELL W. H. P. (1964) Lymphangiomatous malformation of the thoracic duct associated with chylous pleural effusion. *Ann. Surg.* **159**, 180–184.

SABIN F. R. (1902) On the origin of the lymphatic system. *Am. J. Anat.* **1**, 362.

STEWART C. A. and LINNER H. P. (1926) Chylothorax in a newborn infant. *Am. J. Dis. Child.* **31**, 654–656.

SUNDAL B., GUINEY E. J. and O'DONNELL B. (1975) Congenital 'H' type tracheo-oesophageal fistula. *Arch. Dis. Child.* **50**, 862–863.

VAN PERNIS P. A. (1949) Variations of the thoracic duct. *Surgery* **26**, 806–809.

WATERSTON D. J., CARTER R. E. B. and ABERDEEN E. (1962) Oesophageal atresia: tracheo-oesophageal fistula. *Lancet* **1**, 819–822.

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Statistics in *The British Journal of Surgery*

It is part of the clinical scientist's stock-in-trade to use statistical methods. In many instances, and by most readers, these can be taken on trust, but in that there is a wide variety of tests and, on occasion, disagreement amongst both amateurs and professionals on the best choice, it is always wise that authors quote the method used. It is indeed journal policy to quote methods, the reason for their choice and, in the case of clinical trials, the confidence or tolerance limits of the observed results. Delay in acceptance may occur if contributors do not include these details.

Br. J. Surg. Vol. 66 (1979) 488

Intra-abdominal chylous cyst treated by cyst-duodenostomy

GEORGE W. JOHNSTON*

CHYLOUS cysts are very rare and are usually intrathoracic in position. In 1971 Beasley and Mills reported the successful resection of a chylous cyst from the posterior mediastinum and were able to trace only 9 other cases in the literature, the majority being found incidentally in the thorax at autopsy. This paper reports the successful treatment of an intra-abdominal chylous cyst.

Case report

F. N., a white male, first presented at the age of 35 with a 2-year history of typical symptoms of duodenal ulceration. Barium studies confirmed the diagnosis and medical therapy was instituted. The patient's symptoms became more severe over the next year and surgery was advised. At operation a chronic posterior duodenal ulcer was noted and proximal gastric vagotomy without a drainage procedure was performed. The postoperative course was smooth and the patient remained symptom-free for 1 year. He then presented with acute pain in the right hypochondrium, radiating through to the back. On clinical examination a smooth swelling was noted in the right hypochondrium and a provisional diagnosis of mucocoele of the gallbladder was considered; however, the cholecystogram was normal. Barium studies demonstrated narrowing and anterior displacement of the second and third parts of the duodenum (*Fig.* 1) and endoscopy revealed a hold-up of food in the first part of the duodenum but no mucosal lesion. An insulin test was negative using multiple criteria and serum gastrin and glucagon levels were normal. Liver scan showed some indentation of the inferior aspect of the right lobe. Lymphangiography showed no lymph node abnormality or obstruction to flow but an inferior vena cavogram demonstrated marked compression of the vein from L3 to L1. Since the mass was rapidly increasing in size and becoming much more painful laparotomy was undertaken. At operation the patient was found to have a cystic swelling, about 15 cm in diameter, lying retroperitoneally posterolateral to the second part of the duodenum. The capsule of the cyst was firmly adherent to the duodenum, colon and liver; resection was deemed hazardous. Needle aspiration produced milky fluid which was extractable by organic fat solvents and proved to be chyle. The cyst was treated by internal drainage, the medial wall of the cyst being anastomosed to the lateral wall of the second part of the duodenum, establishing a 1-cm stoma. Biopsy of the cyst wall revealed only dense fibrous tissue with chronic inflammatory cell infiltration. The postoperative course was smooth and there has been no recurrence of symptoms or swelling during follow-up, which extends for more than 3 years.

Discussion

A number of cases of chylous ascites have been reported after truncal vagotomy (Cox et al., 1966; Clain, 1971; Musgrove, 1972). In each instance the accumulation of chylous ascites was noted within 2 weeks of operation and in each case was shown to be due to division of an aberrant lymph channel in the region of the abdominal oesophagus. In this patient the long interval between the vagotomy and the appearance of the cyst makes it more difficult to associate the two events. Possibly damage to a branch of the cisterna chyli in the oesophageal region at the time of vagotomy allowed chyle to track down retroperitoneally behind the lesser sac to the paraduodenal site, and there slowly produce a chylous pseudocyst.

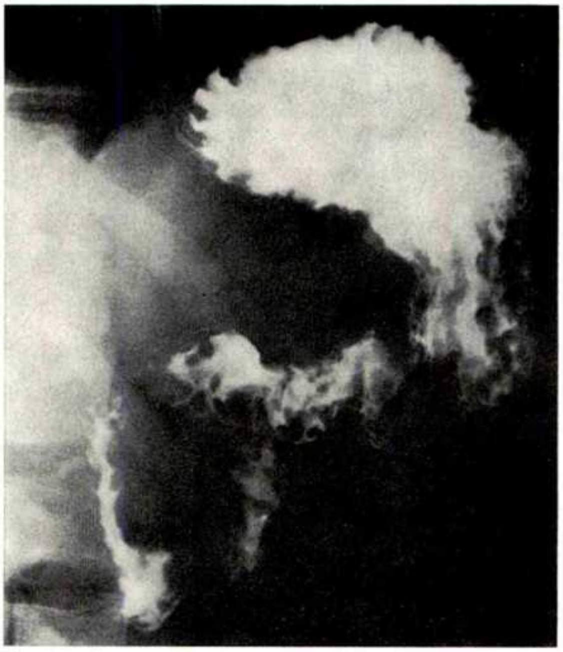

Fig. 1. Barium meal showing compression and anterolateral displacement of the second part of the duodenum.

The chief problem was that of operative management. Excision of the cyst or pseudocyst would have been extremely dangerous because of the absence of planes of dissection and external drainage would probably have produced a troublesome fistula. Because of the high success rate with internal drainage in the case of pancreatic pseudocysts it was decided to use the same principle for this chylous cyst. Cyst–duodenostomy was effective in relieving the patient's signs and symptoms and this success has been maintained in the long term.

References

BEASLEY W. E. and MILLS M. (1971) Chylous cystectomy with prosthetic reconstruction of the diaphragm and oesophageal hiatus. *J. Thorac. Cardiovasc. Surg.* **61**, 324–329.

CLAIN A. (1971) Chylous ascites following vagotomy. *Br. J. Surg.* **58**, 312–314.

COX W. D., SCHMITZ R. L. and GILLESBY W. J. (1966) Unusual complication of vagotomy and pyloroplasty—chylous ascites and achalasia: case reports. *Am. Surg.* **32**, 259–260.

MUSGROVE J. E. (1972) Post-vagotomy abdominal chylous fistula. *Ann. Surg.* **175**, 67–69.

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Absorption from the jejunum is increased by forward and backward pacing*

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SUMMARY

In 4 dogs a 75-cm segment of jejunum was isolated from the intestinal stream. Stimulating electrodes were implanted at each end of the segment and recording electrodes at intervals between. The two ends of the segment were fashioned as stomas on the anterior abdominal wall. After recovery, the electrical activity of the segment was continuously recorded, whilst a solution of 100 mmol/l glucose and 90 mmol/l NaCl was infused into the proximal stoma at 2·9 ml/min. Effluent from the distal stoma was collected in 5-min aliquots for three consecutive 30-min periods. In the second period electrical stimuli were given via either the proximal or the distal bipolar electrodes to entrain pacesetter potentials. Both forward and backward electrical pacing decreased the output of water, glucose and sodium from the jejunal segment, but the decrease was significantly greater with backward pacing. We conclude that pacing a segment of jejunum backwards with electrical stimuli produces a greater increase in absorption from the segment than pacing it forwards, a finding which has therapeutic implications in patients with the short bowel syndrome.

PATIENTS who have undergone resection of large portions of small intestine have rapid intestinal transit and suffer from malabsorption, steatorrhea and excessive faecal output of water and electrolytes (Winawer et al., 1966). Treatment of this 'short bowel syndrome' is difficult and often unsuccessful. An effective, safe method of slowing transit through the small bowel and enhancing absorption would be of considerable benefit.

An attractive hypothesis is that intestinal transit can be slowed and intestinal absorption increased by pacing the pacesetter potentials of the small intestine with electrical stimuli.

The pacesetter potentials are omnipresent, regularly recurring, cyclical changes in electrical potential found in the small intestine of both the dog and man (Sarna, 1975). The cycles are generated by a pacemaker located within the first centimetre of the duodenum (Hermon-Taylor and Code, 1971), from where they propagate distally to the remaining small bowel. As they sweep distally, the pacesetter potentials phase the onset of a second type of electrical activity, called action potentials (Sarna, 1975), which in turn triggers intestinal contractions. In this way, the pacesetter potentials set the pattern of intestinal contractions and regulate the transit of content through the small bowel.

Bunker et al. (1967) have shown that the frequency of the pacesetter potentials is identical in the proximal 10–30 per cent of the canine small intestine, while from the mid-jejunum to the terminal ileum the frequency gradually declines. Along the proximal plateau of identical frequency electrical stimuli can entrain pacesetter potentials, increase their frequency and even reverse their direction of propagation (Akwari et al., 1975). Such backward pacing, in turn, reverses the direction of propagation of intestinal contractions along the plateau and slows the transit of content through the paced segment (Kelly and Code, 1977). Pacesetter potentials along the distal frequency gradient can also be entrained if the distal bowel is separated from the duodenal pacemaker by intestinal transection.

We have previously shown (Collin et al., 1977) that backward electrical pacing of an isolated jejunal segment results in prolongation of transit and increased absorption from the segment. The aim of the present study was to determine whether a similar increase in absorption could be produced by forward electrical pacing and to compare changes in absorption with forward and backward pacing.

Methods

Four female mongrel dogs of 13–17 kg were used in the study. In each dog, under pentothal anaesthesia (30 mg/kg) and using aseptic operating technique, a 75-cm segment of jejunum located 50–125 cm from the pylorus was isolated, and the anatomical continuity of the remaining bowel re-established by end-to-end anastomosis. A bipolar stimulating Ag–AgCl electrode was sewn to the serosal surface of the isolated segment 7·5 cm from each end and monopolar recording electrodes were attached at 10-cm intervals between (*Fig. 1*). The electrodes were connected by insulated copper wires to a multipinned socket mounted within a stainless-steel cannula which was fixed to the abdominal wall. The two ends of the segment were fashioned as separate stomas on the anterior abdominal wall. The dogs were allowed a minimum of 7 days to recover from the operation.

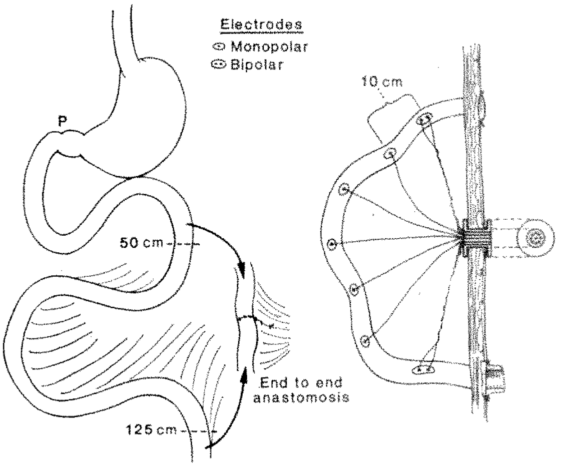

Fig. 1. Preparation of an isolated 75-cm segment of proximal jejunum.

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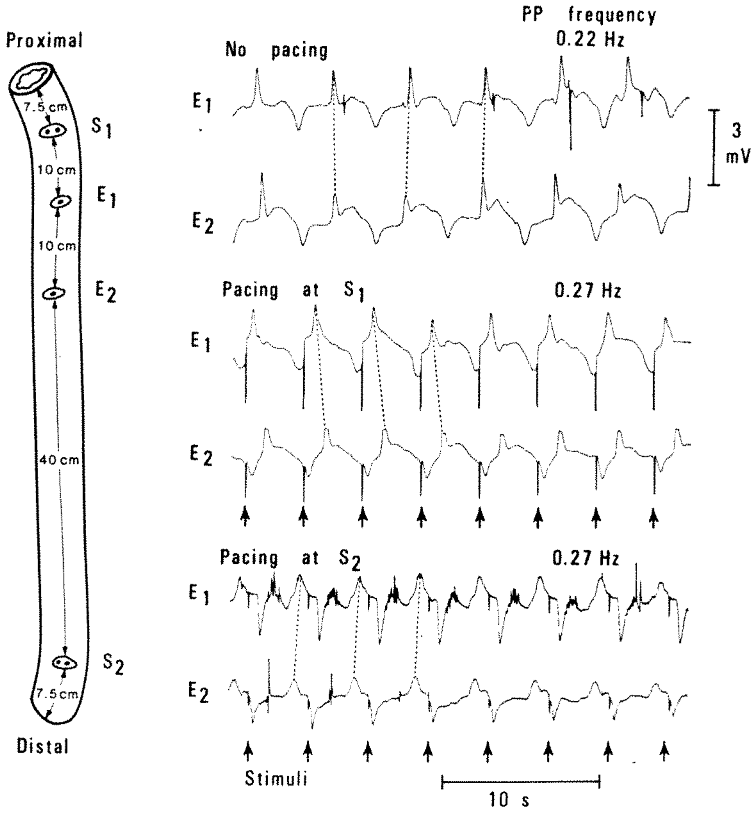

Fig. 2. Electrical pacing at both proximal and distal sites of stimulation (S) increases the frequency of the pacesetter potentials (PP), but the PP propagate distally during proximal pacing and proximally during distal pacing. *E*, recording electrode; dotted lines show direction of PP propagation; arrows, stimulus artefact.

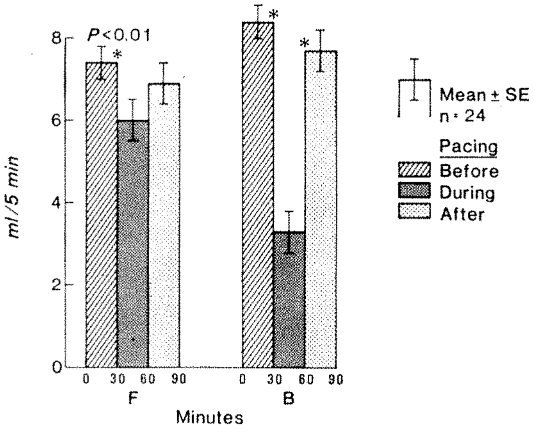

Fig. 3. The effects of forward and backward electrical pacing on the volume output from the distal stoma of the jejunal segments. F, forward pacing; B, backward pacing. * Mean differs from that during pacing. Comparison of F and B, $P<0{\cdot}001$.

In each experiment 50 g of raw liver were fed to the fasted, conscious dog to induce a fed pattern of intestinal electrical activity and to abolish the interdigestive myoelectric complex (Mroz and Kelly, 1977). A 16-French Foley catheter with a 5-ml balloon was passed into the oral end of the segment through its proximal stoma and the balloon inflated in order to prevent loss of fluid from the proximal stoma during the experiment. The segment was next gently irrigated with 100 ml of isotonic sodium chloride to clear the lumen of debris. A solution containing 100 mmol/l glucose and 90 mmol/l sodium chloride (osmolality, 280 mosmol/l, pH 5·3) was then continuously infused through the catheter into the oral end of the segment at 2·9 ml/min. Thirty minutes of infusion were allowed for steady state conditions to be established, after which effluent from the distal stoma was collected in 5-min aliquots for three consecutive 30-min periods. The electrical activity of the jejunal segment was recorded throughout the experiment using a Gould Brush recorder, model 260, with the AC amplifiers set at a time constant of 1 s.

In six experiments in each dog in the second 30-min period electrical stimuli (frequency 0·27 Hz, duration 50 ms, amplitude 4 mA) were given via the proximal bipolar electrode to drive the isolated segment forward. In a further six experiments in each dog electrical stimuli were given via the distal bipolar electrode to drive the segment backward. Stimuli were generated by a model 800 digital pulse generator (WP Instruments). The volume of each 5-min aliquot of effluent was recorded and the glucose, sodium and potassium concentrations measured. The mean volume and output of glucose, sodium and potassium per 5 min were calculated for each 30-min period. Statistical analyses were carried out using the paired *t* test. Differences between the means of the three periods were analysed separately for the two groups of experiments. The mean outputs with forward and with backward pacing were then compared.

In 18 experiments involving forward pacing and in 18 experiments involving backward pacing a bolus of ^{14}C polyethylene glycol (PEG, mol. wt ~4000) was injected in the period before pacing and a further bolus during pacing. The first bolus had passed completely through the loop by the time the second bolus was given. The time taken for 20 per cent excretion of each bolus of ^{14}C PEG was determined and used as a measure of transit.

Results

In all experiments electrical stimulation at the proximal or the distal bipolar electrode during the second 30-min period consistently entrained the pacesetter potentials of the jejunal segment. Before pacing, the rhythm of the pacesetter potentials of the segment was irregular, their frequency variable (range 0·22–0·26 Hz, mean ± s.e. mean 0·24 ± 0·02 Hz) and the direction of their propagation inconsistent (*Fig.* 2). However, during pacing the rhythm of the pacesetter potentials was regular, their frequency was steady and increased to that of the stimulation frequency (0·27 Hz) and their direction of propagation was consistent. When pacing at the proximal site, pacesetter potentials were propagated in a distal direction—from the site of stimulation to the aboral end of the segment. However, when pacing at the distal site, the pacesetter potentials were propagated in the reverse direction—from the site of stimulation to the orad end of the segment.

The volume of output from the distal stoma during the 30 min of forward pacing (mean ± s.e. mean = 6·0 ± 0·5 ml/5 min) was slightly decreased compared to the 30 min before pacing (7·4 ± 0·4 ml/5 min) ($P <$ 0·001). Glucose output during forward pacing (0·48 ± 0·004 mmol/5 min) was also slightly decreased ($P <$ 0·02) compared with the period before pacing (0·56 ± 0·03 mmol/5 min). A similar small decrease in output from the distal stoma during forward pacing was observed for sodium (0·74 ± 0·04 to 0·58 ± 0·04 mmol/5 min, $P <$ 0·01) and for potassium (0·024 ± 0·001 to 0·020 ± 0·001 mmol/5 min, $P <$ 0·02). However, mean transit time during forward pacing (6·5 ± 1·9 min) was not significantly different from before pacing (3·2 ± 0·6 min) ($P <$ 0·1).

During backward electrical pacing fluid, glucose, sodium and potassium output were all markedly decreased compared with both the 30-min periods before and after pacing ($P <$ 0·001). Moreover, the transit time was longer during backward pacing (9·2 ± 2·7 min) than before pacing (2·3 ± 0·3 min) ($P <$ 0·05).

Comparisons were made between the output from the distal stoma during forward pacing and backward pacing of the jejunal segment. During backward electrical pacing output was significantly less than during forward pacing for water ($P <$ 0·001) (*Fig.* 3), glucose ($P <$ 0·001) (*Fig.* 4), sodium ($P <$ 0·01) (*Fig.* 5) and potassium ($P <$ 0·01) (*Fig.* 6).

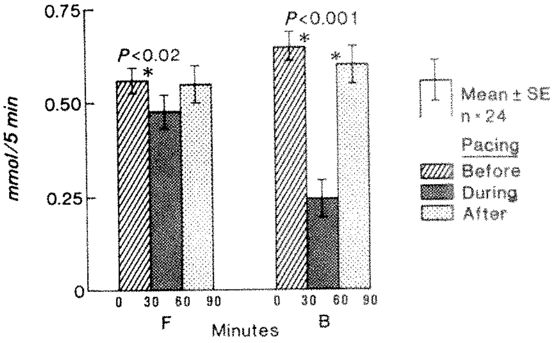

Fig. 4. The effects of forward and backward electrical pacing on the output of glucose from the distal stoma of the jejunal segments. F, forward pacing; B, backward pacing. * Mean differs from that during pacing. Comparison of F and B, $P <$ 0·01.

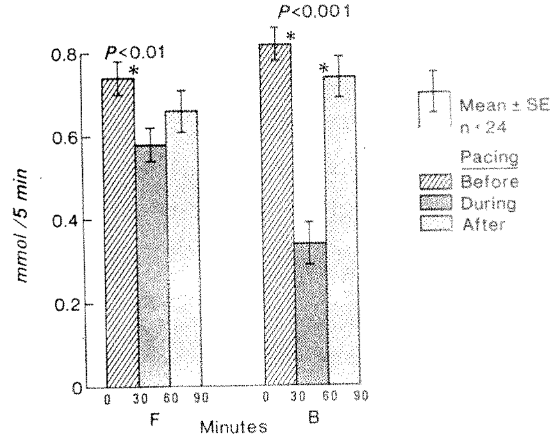

Fig. 5. The effects of forward and backward electrical pacing on the output of sodium from the distal stoma of the jejunal segments. F, forward pacing; B, backward pacing. * Mean differs from that during pacing. Comparison of F and B, $P <$ 0·01.

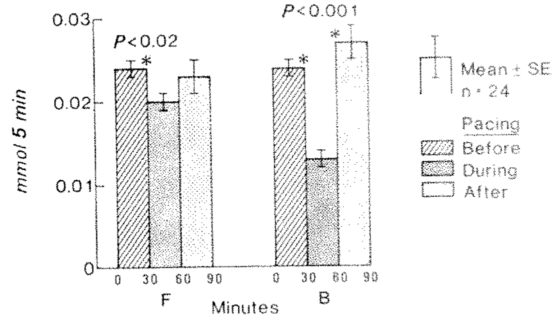

Fig. 6. The effects of forward and backward electrical pacing on the output of potassium from the distal stoma of the jejunal segments. F, forward pacing; B, backward pacing. * Mean differs from that during pacing. Comparison of F and B, $P <$ 0·01.

Discussion

It has previously been shown that application of appropriate electrical stimuli to the small intestine can entrain pacesetter potentials, increase their frequency and result in propagation of pacesetter potentials from the site of stimulation to more distant bowel (Akwari et al., 1975). These experiments demonstrate that in a segment of proximal jejunum entrainment can also be consistently achieved and can be maintained for at least 30 min.

The mechanism as to why such entrainment leads to increased absorption during forward pacing is not clear. Gregory (1950) showed that increasing the contractile frequency along a length of small intestine slowed transit of content through that length. It might be expected, therefore, that an increase in pacesetter potential frequency, and hence of action potential and contraction frequency, would slow transit, which might in turn increase absorption by prolonging contact of the intestinal content with jejunal mucosa. However, transit was not consistently slowed during forward pacing. None the less, the explanation for the enhanced absorption with forward pacing may be related to an increased contractile frequency produced by the pacing. More likely is that increased contractile frequency effectively stirs intestinal content, disrupting the barrier to absorption posed by the unstirred layer of content adjacent to the mucosa. Absorption could thereby be enhanced. Experiments measuring motor activity during forward pacing are required.

The mechanism of the more marked enhancement of absorption with backward pacing as compared to forward pacing seems likely to be related to the orad propagation of the pacesetter potentials produced by backward pacing. Both forward and backward pacing regularized the rhythm and direction of propagation of the pacesetter potentials and increased the frequency of the pacesetter potentials to that of the pacing stimuli, but only backward pacing resulted in propagation of the cycles in an orad direction. Such orad propagation of cycles, hence of contractions, slows or reverses transit of content through the bowel, as reported by us in past papers (Collin et al., 1977; Kelly and Code, 1977) as well as in the present paper. Thus, backward pacing might enhance absorption not only by bringing about more effective stirring of intestinal content because of an increased contractile frequency, but also by slowing transit and prolonging contact of content with the intestinal epithelium.

If similar increases in absorption can be produced by electrical pacing of the intact human bowel, these experiments would point to an intriguing new technique for the treatment of those patients suffering from the serious nutritional, fluid and electrolyte problems of the short bowel syndrome.

Acknowledgememts

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References

AKWARI O. E., KELLY K. A., STEINBACH J. H. et al. (1975) Electric pacing of intact and transected canine small intestine and its computer model. *Am. J. Physiol.* **229**, 1188–1197.

BUNKER C. E., JOHNSON L. P. and NELSEN T. S. (1967) Chronic *in situ* studies on the electrical activity of the small intestine. *Arch. Surg.* **95**, 259–268.

COLLIN J., KELLY K. A. and PHILLIPS S. F. (1977) Electrical pacing increases jejunal absorption of water, glucose and sodium. *Surg. Forum* **28**, 428–430.

GREGORY R. A. (1950) Some factors influencing the passage of fluid through intestinal loops in dogs. *J. Physiol.* **111**, 119–137.

HERMON-TAYLOR J. and CODE C. F. (1971) Localization of the duodenal pacemaker and its role in the organization of duodenal myoelectric activity. *Gut* **12**, 40–47.

KELLY K. A. and CODE C. F. (1977) Duodenal-gastric reflux and slowed gastric emptying by electrical pacing of the canine duodenal pacesetter potential. *Gastroenterology* **72**, 429–433.

MROZ C. T. and KELLY K. A. (1977) The role of the extrinsic antral nerves in the regulation of gastric emptying. *Surg. Gynecol. Obstet.* **145**, 369–377.

SARNA S. K. (1975) Gastrointestinal electrical activity: terminology. *Gastroenterology* **68**, 1631–1635.

WINAWER S. J., BROITMAN S. A., WOLOCHOW D. A. et al. (1966) Successful management of massive small bowel resection based on assessment of absorption defects and nutritional needs. *N. Engl. Med. J.* **274**, 72–78.

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An experimental evaluation of segmental reversal after massive small bowel resection

AIRES A. B. BARROS D'SA*

SUMMARY

The technique of reversal of a distal segment of residual small intestine was applied to the management of massive resection. A controlled evaluation was carried out in dogs into the effects of segmental reversal on the proximal remnant after the distal 75 per cent of the small bowel had been resected. The variables studied were survival, body weight, glyceryl tri(palmitate-1-^{14}*C) absorption and mouth-to-caecum transit time. Animals subjected to resection alone had accelerated intestinal transit, poor absorption, serious weight loss and a high early mortality. It was clearly demonstrated that segmental reversal after resection produced marked and progressive delay in transit time from mouth to caecum, sustained improvement in fat absorption and body weight and enhanced survival.*

MASSIVE small bowel resection may be necessary for mesenteric thromboembolic disease, Crohn's disease and trauma (Colcock and Braasch, 1968). Although the operation itself is neither difficult nor exacting, the consequences are serious. While occasional cases of survival after such an extensive ablative procedure have been documented (Kinney et al., 1962), the operation has a high mortality (Simons and Jordan 1969) and the well-recognized short bowel syndrome is common postoperatively. This is characterized by rapid intestinal transit, severe diarrhoea, steatorrhoea, general impairment of absorption and precipitous decline in health. Sequelae such as gastric hypersecretion and accelerated transit are poorly understood but humoral theories have been advanced to explain the mechanism of their occurrence (Wright and Tilson, 1973; Barros D'Sa and Buchanan, 1977).

The diverse pathophysiological problems encountered after massive bowel resection pose great difficulties in management (Barros D'Sa et al., 1978). Despite advances in modern therapy and postoperative care many patients still succumb after massive intestinal resection (Barros D'Sa, 1979) and this has stimulated the experimental trial of several surgical procedures (Budding and Smith, 1967; Sadowski, 1967; Schiller et al., 1968; Hidalgo et al., 1973). The technique of segmental reversal has been tried in the surgical management of the dumping syndrome after gastric resection (Poth, 1957), in treating post-vagotomy diarrhoea (Craft and Venables, 1968), in preventing rapid evacuation after total or partial colectomy (Burrows et al., 1965) and for ileostomy dysfunction (Ellis and Coll, 1968) and even in limiting severe chronic diarrhoea with some success (Madding et al., 1965).

Reversed segments have had minimal clinical trial in the treatment of massive resection and the short bowel syndrome (Hollender et al., 1972). Against a background of conflicting experimental data, Gibson et al. (1962) were the first to apply the procedure successfully in a patient who had undergone extensive bowel resection. While some reports were favourable (Venables et al., 1966; Fink and Olson, 1967), others were inconclusive and lack adequate clinical evaluation (Madding et al., 1965; Blades and Peple, 1970). Of 29 reports, the nutritional results have been satisfactory to excellent in 23 cases (Barros D'Sa, 1975a). Firm evidence of the safety and efficacy of segmental reversal is required before its clinical use can be justified.

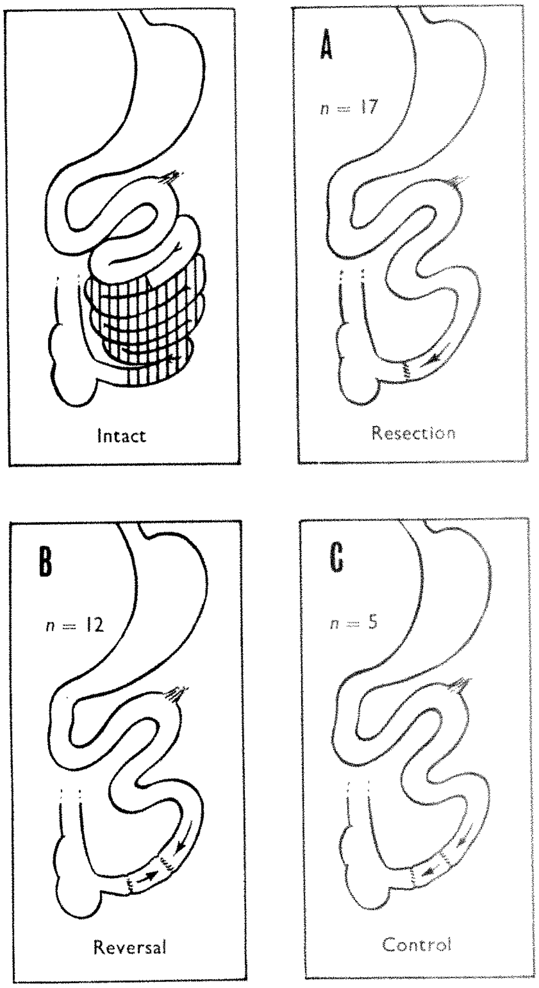

Fig. 1. Experimental models prepared to evaluate the function of reversed segments after massive intestinal resection. The extent of resection is represented by a hatched area.

The objective of this study, therefore, was to carry out a controlled evaluation of the function and usefulness of reversal of a segment in the remnant after massive small bowel resection.

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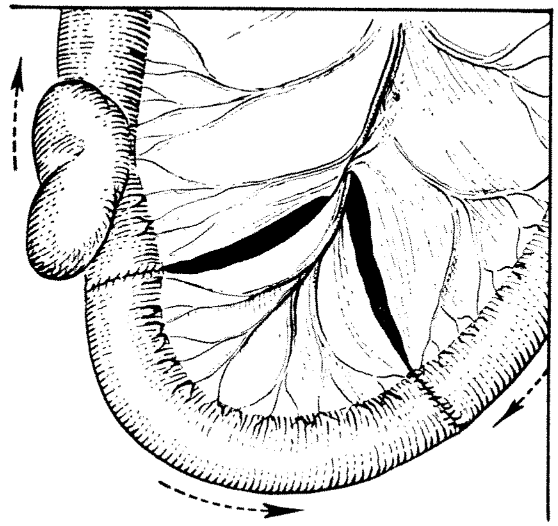


Fig. 2. Technique of construction of a reversed segment in the terminal jejunal remnant (with the ileal stump, caecum and ascending colon distally). Arrows indicate polarity.

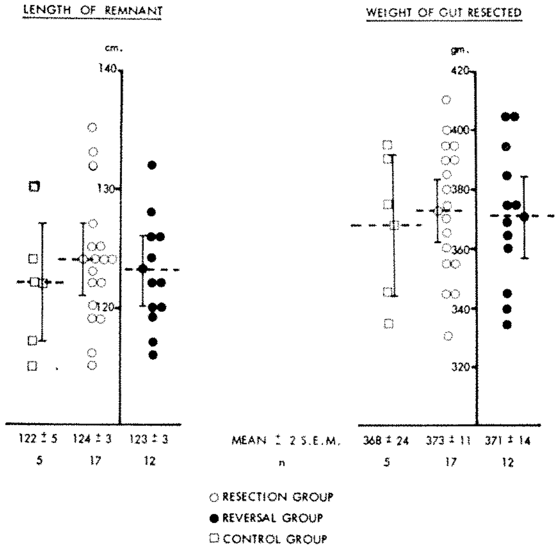


Fig. 3. Data obtained at operation: length of small bowel remnant, and weight of gut resected (75 per cent distal small bowel resection in every case).

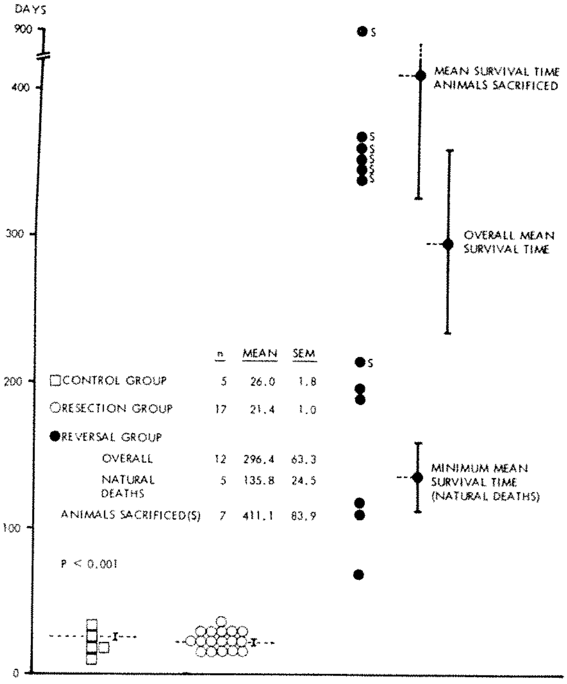
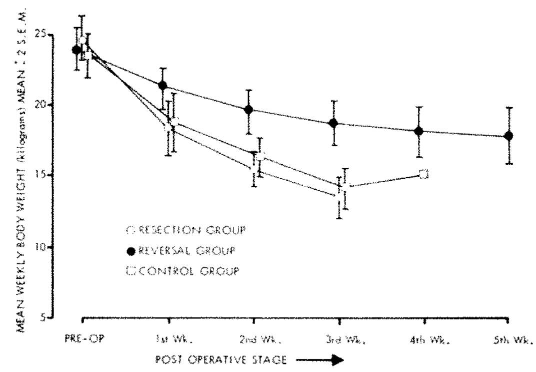


Fig 4. Survival time in the control, resection and reversal groups.



REVERSAL v RESECTION	NS	P < 0.05	P < 0.01	P < 0.01
REVERSAL v CONTROL	NS	NS	P < 0.01	P < 0.01

Fig. 5. Mean weekly body weights: preoperative and first 5 postoperative weeks.

Material and methods

Plan of study

The design of the experiments was as follows. Three dog models, as represented diagrammatically in *Fig.* 1, were prepared and all animals had 75 per cent distal small bowel resections. The first, with resection alone, formed the 'resection' group; the second, with a reversal of the terminal 10 cm of the remnant, formed the 'reversal' group; the third, a specially prepared 'control' group, had the terminal 10 cm isolated and anastomosed without reversal.

The following variables were assessed in these three groups: (*a*) survival after operation; (*b*) body weight before operation and at weekly intervals thereafter; (*c*) fat absorption preoperatively and at intervals after operation, using ^{14}C-labelled glyceryl tripalmitate in the breath analysis technique (the sampling apparatus was modified for use in dogs); (*d*) mouth-to-caecum transit time was measured by radiological screening using a contrast meal before operation and at intervals thereafter.

Due to the number of variables being investigated, (*b*), (*c*) and (*d*) were studied in 7 dogs of the resection group and 7 of the reversal group, all of which were unselected, and in the 5 dogs of the control group. Survival time was recorded in an additional 10 dogs of the resection group and 5 of the reversal group. The results were analysed by comparison of one group with each of the other two using the Student's *t* test.

Material

Registered female greyhounds, aged between 1½ and 2½ years and weighing between 20 and 28 kg, were vaccinated against distemper, cleared of external parasites and wormed. Intravenous Nembutal (pentobarbitone sodium) anaesthesia was employed in a dosage of 26 mg/kg body weight.

The abdomen was opened through a midline incision. Handling of the bowel was avoided before measurement. The ligament of Treitz was identified and the bowel carefully measured along its antimesenteric border, without stretching it, from this point down to the ileocaecal junction using a flexible ruler. The technique allowed reproducible measurements of length to be made. A routine resection of 75 per cent of the distal small bowel was performed, preserving the proximal 25 per cent. A 3-cm length of the ileal stump was also preserved to permit a comfortable end-to-end anastomosis, using a single layer of 3/0 atraumatic chromic catgut with an over-and-over all-coats suture locking every third stitch. This technique was used to prevent, as far as possible, undue invagination or inversion with possible narrowing at the suture line. Any tendency to produce a mechanical impediment to intraluminal flow was thus avoided, a factor of importance in the study. The mesentery was reconstituted. *Fig.* 1(*a*) represents the completed resection group model.

In those dogs that were to have a reversed segment, the terminal 10 cm of the proximal 25 per cent of small bowel was carefully measured along its antimesenteric border after ensuring that this segment was supported by an adequate vascular pedicle. In all cases, a secondary arcade of vessels arising from the primary mesenteric vessels was selected. After resection of the distal 75 per cent of small bowel, transection was effected on a line 10 cm proximal to the end of the remnant, and at this point the mesentery was divided down to the base of the secondary vascular arcades. Employing the mesenteric pedicle as an axis, the 10-cm segment was then rotated through 180° in a clockwise direction so that its proximal end lay opposed to the ileal stump and its distal end to the proximal remnant of the intestine. No occlusion of the blood supply resulted from this manoeuvre. Pulsation in the vascular pedicle and the colour of bowel adjacent to the anastomotic suture were checked before abdominal closure and found to be satisfactory. *Fig.* 2 illustrates the reversed segment *in situ*.

The two anastomoses were performed as described above and the mesenteric defects closed. There was no evidence of ischaemia at the anastomoses. The completed reversal model is illustrated in diagrammatic form in *Fig.* 1(*b*).

In the control group the same technique as adopted in the preparation of the reversal model was used up to the point of transection 10 cm proximal to the tip of the remnant. After that stage, the two anastomoses were carried out without reversing the isolated segment, and the mesentery was left intact. *Fig.* 1(*c*) is a diagrammatic representation of this control model.

The fluid regimen was as follows: 1 litre 5 per cent dextrose/0·5 N saline during the operation; a total of 1·5 litres of 0 5 N saline subcutaneously on each of the first 2 postoperative days; 1 litre 5 per cent dextrose and 0·5 litre N saline intravenously during the day, and 0 5 litre of 0·5 N saline subcutaneously in the evening on the next 3 days. On the sixth postoperative day, oral intake was commenced with milk and water and by the eighth day solid feeding with two 400 g tins of meat ('Lassie Meaty Chunks' Pedigree Petfoods) per day was established. When oral feeding in this quantity was not tolerated by a dog in any group, adequate fluid, caloric and electrolyte needs were provided parenterally, based on the general condition of the animal, the urinary and faecal output and the biochemical analysis of serum electrolytes.

Survival after operation was recorded in the three groups. Animals were weighed preoperatively and at weekly intervals throughout their period of survival; morning fasting weights were recorded.

The breath analysis technique of studying fat absorption by interval sampling of expired air was used (Kaihara and Wagner, 1968). A breath sampler unit was designed with suitable modifications for use with greyhounds. The principle of the device was simply to channel the animal's dried expired air into a breath sampling solution in which CO_2 was 'trapped'. A disposable polythene facemask, fitting comfortably over the dog's head, was attached to the gas inlet of a Ruben (British Oxygen Co. Ltd) non-rebreathing valve allowing the animal to inspire room air freely. The gas outlet of the valve was connected to the drying and trapping section of the apparatus so that all exhaled air ultimately flowed into a sampling vial. This breath sample unit functioned well.

Dogs fasting overnight were weighed. The carrier solution of corn oil was prepared at 5 ml/kg body weight less 20 ml, this being the volume containing the 5 μCi of ^{14}C-labelled fat in the form of glyceryl tri(palmitate-1-^{14}C) (Radiochemical Centre, Amersham). The dose and rinsings with carrier solution were completely ingested. The animals were caged to ensure a resting state and constant metabolic conditions during the test. Eight-hourly breath samples were collected, commencing an hour after giving the dose. Animals accepted the sampler unit and their breathing was steady. Radioactivity in samples was measured and the results of absorbed fat were calculated and expressed as percentage ^{14}C fat dose/mmol CO_2 expired $\times 10^{-4}$.

Mouth-to-caecum transit time was studied radiologically. A standard 250 g of the dog food was used as the test meal. To avoid errors in transit time caused by barium, only 20 g of stable suspension of 95 per cent w/v barium sulphate (Micropaque) were added to the meal which emulsified before administration to fasting dogs. The time of ingestion was noted and the abdomen was screened using an image intensifier to monitor the progress of the meal. The times taken for the head of the food column to arrive at the caecum and for the tail of the column of meal to leave the ileum finally were recorded. Observations were also made of bowel calibre and direction of propulsion of its contents, with particular reference to the behaviour of the reversed segment.

Results

Operation data

The three groups were found to be statistically comparable, the following measurements having been recorded from each animal: (*a*) total length of small bowel, defined as that part between the ligament of Treitz and the ileocaecal junction; (*b*) length of 75 per cent distal small bowel resected; (*c*) length of the jejunal remnant; and (*d*) weight of the gut resected (checked immediately on removal). The two important measurements of length of jejunal remnant and weight of gut resected are plotted in *Fig.* 3.

Survival

The length of survival of individual animals is plotted in *Fig.* 4 and mean survival times are shown.

The resection group had a mean survival time of 21 days and no animal lived for more than 30 days. Survival in the control group was marginally longer with a mean time of 24 days but the difference was not significant. In the reversal group, those dogs that died naturally had a minimum mean survival time of 136 days, no dog dying before 68 days had elapsed. This time is significantly greater than that of either resection or control groups ($P < 0\ 001$). Six healthy animals of the reversal group, clearly in good health, were sacrificed between 213 and 900 days. These 6 dogs, as well as one which was reoperated to remove the reversed segment, together survived to a mean time of 411 days. Taken together, animals in the reversal group survived to a mean of 296 days, which was far greater than that of the control or resection groups. The mean survival time for the reversal group could have been much longer had there been no intervention.

Body weight

All dogs suffered catastrophic weight loss, the amount and rate of weight loss in the resection group being especially high, in spite of fluid replacement, high calorie parenteral nutrition and supplements. Losses in the reversal group were at a consistently lower rate, levelling off before a later gradual weight increase.

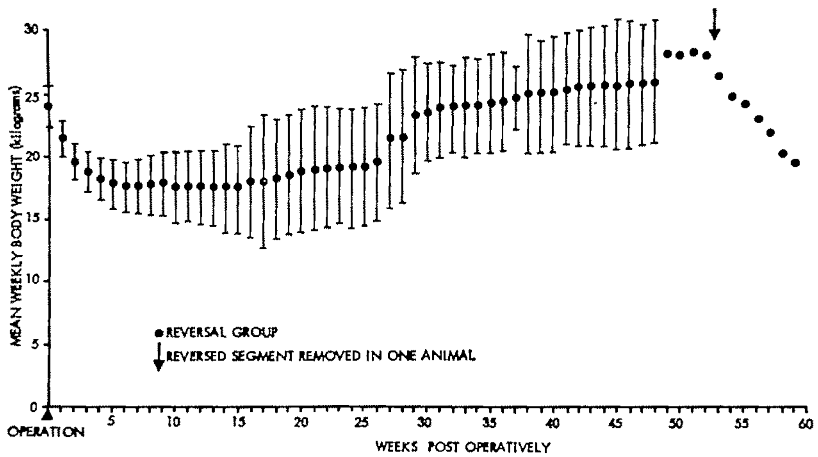


Fig. 6. Mean weekly body weight in reversal group.

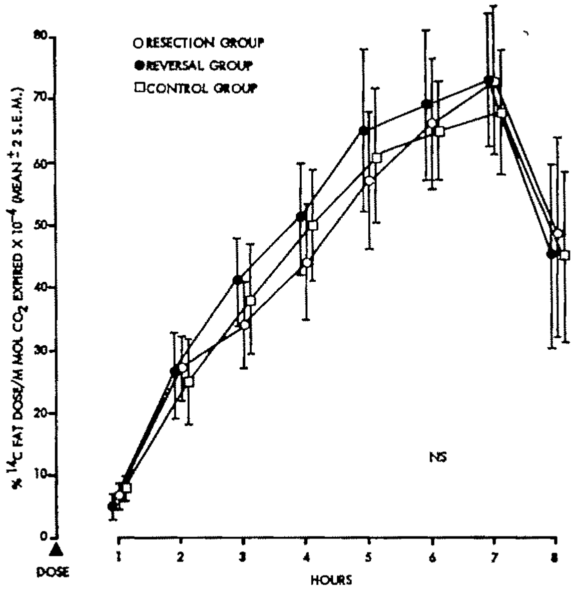


Fig. 7. Glyceryl tri(palmitate-1-^{14}C) absorption. Preoperative results in the three groups.

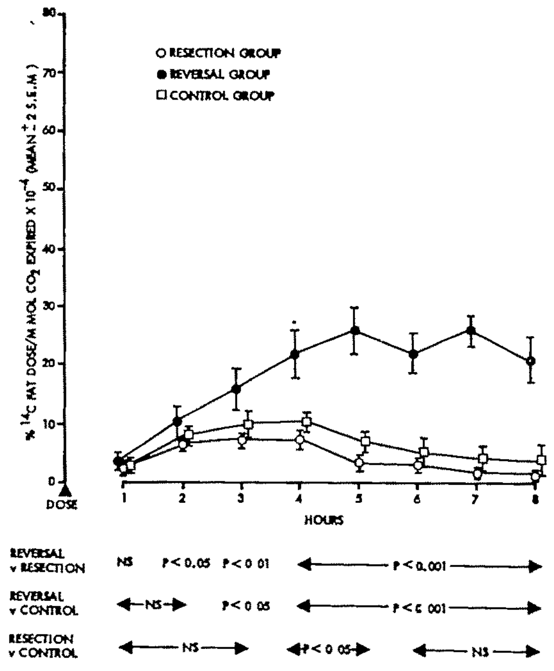


Fig. 8. Glyceryl tri(palmitate-1-^{14}C) absorption. Results in each group 3 weeks postoperatively.

The mean weekly body weights of these groups over the first 5 postoperative weeks give an indication of differential weight loss (*see Fig.* 5). The similar behaviour in the control and resection groups is clearly revealed. The reversal group showed significantly less weight loss than the resection and control groups from the first and second postoperative weeks respectively ($P<0{\cdot}05$ to $P<0{\cdot}01$).

The overall progress of animals in the reversal group can be observed in *Fig.* 6. The greatest mean loss of 6·5 kg occurred at 15 weeks after which there was a steady rise to preoperative levels by 33 weeks. In order to test the value of segmental reversal in accounting for this recovery, the reversed segment in one dog was excised. This particular animal had already exceeded its initial preoperative weight by nearly 1 kg when it was reoperated 1 year later. After reoperation, its weight fell precipitously, a pattern encountered in animals of the resection group.

Glyceryl tri(palmitate-1-^{14}C) absorption

Studies were carried out preoperatively and 3 weeks after operation. As dogs in the reversal group survived, testing was continued at 6, 9, 15, 20, 25, 30, 40 and 50 weeks postoperatively.

The pattern of fat absorption in the three groups before operation is demonstrated in *Fig.* 7. All groups gave comparable results and there were no significant differences between any two groups at each hour of testing. The same animals were then tested 3 weeks postoperatively. The differences in absorption at this stage in relation to preoperative results are striking, and these are illustrated in *Fig.* 8. Marked diminution in absorption was observed in the resection group and the control group behaved similarly, with very low levels recorded after 4 h. Absorption levels in the

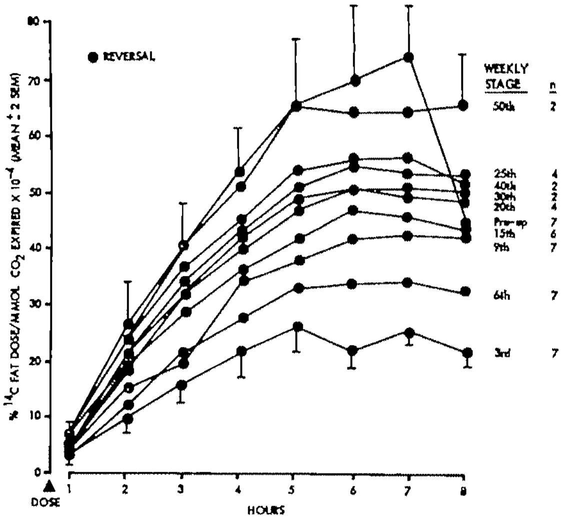


Fig. 9. Glyceryl tri(palmitate-1-^{14}C) absorption. Results preoperatively and at various stages postoperatively in the reversal group.

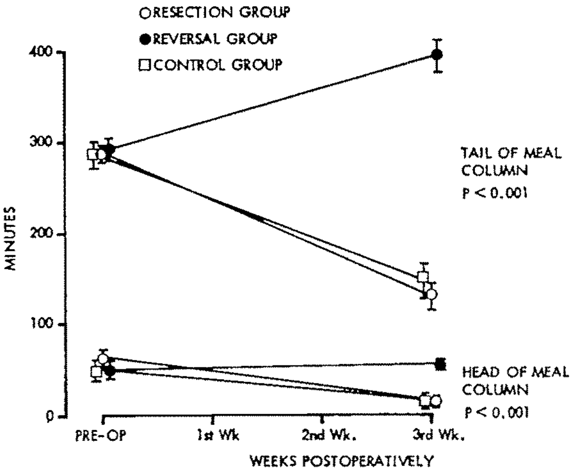


Fig. 10. Mouth-to-caecum transit time. Preoperative and postoperative (third week) results in the three groups.

reversal group also fell well below normal, but these were significantly better than in the resection or control groups, especially after 4 h ($P<0.001$).

Animals of the reversal group survived to be tested repeatedly. An improving ability to absorb fat is clearly demonstrated in *Fig.* 9, this trend progressing with the passage of time. After 15 weeks, absorption levels between 3 and 6 h are comparable to those before operation. After this period, levels remain high, but the number of animals tested was 4, or fewer.

Mouth-to-caecum transit time

These tests were performed preoperatively and 3 weeks after operation. In the reversal group studies were continued at intervals for almost 1 year. Observations of interest during screening were recorded.

The transit rates of the head and tail of the barium column in the three groups are illustrated in *Fig.* 10. *Head of meal column transit time*: All three groups started preoperatively with mean times that were comparable. At 3 weeks after operation, significant falls occurred in the resection group ($P<0.001$) and in the control group ($P<0.01$), but the mean time in the reversal group did not change significantly. However, mean transit time in the reversal group was significantly greater than that of either the resection group or the control group ($P<0.001$).

Tail of meal column transit time: Once again, there was no significant difference among the three groups in the preoperative phase. At 3 weeks the mean transit time in the resection and control groups fell significantly below preoperative values ($P<0.001$), and conversely in the reversal group the mean transit time was longer than preoperative time ($P<0.001$). Quite clearly the mean transit time in the reversal group was significantly longer than that of the resection or control groups ($P<0.001$). It is noteworthy that, in all groups, the alteration in transit rate as a result of operation was greater for the tail than for the head of the meal column.

As several animals in the reversal group survived, further observations of mouth-to-caecum transit times were made at 6, 9, 15, 20, 30, 40 and 50 weeks. The significant delay in transit noted at 3 weeks progressively increased, and at 50 weeks after operation, the mean transit times of the head and tail of the meal column were 50 per cent and 70 per cent respectively above preoperative values.

Observations at screening

Initially, the observed diameters of the jejunal remnant as well as the reversed segment did not suggest dilatation at any stage. In studies done at 40 and 50 weeks, there appeared to be minimal dilatation of the remnant just proximal to the reversed segment, but absence of calibration on the image intensifier made such observations unreliable. Radio-opaque markers placed around each anastomosis permitted a view of motor activity of the reversed segment. There was consistent visual evidence that the reversed segment was physically instrumental in contributing to delay in transit.

As the contrast meal in the jejunal remnant approached and attempted to negotiate the reversed segment, it was halted in the proximal part of the segment distending it. Having shown a reluctance to advance, the meal was promptly squirted back up the jejunal remnant, thus effectively impeding transmission. Distinct repeated and often forceful retrograde flow of the meal was followed by forward propulsion producing a to-and-fro oscillating movement. A little was allowed to pass through into the ileal stump by the reversed segment, so that transit was piecemeal beyond this point. There was no evidence of obstruction in the pathological sense, and the meal emptied slowly into the colon.

Discussion

To be credible, the value of reversed segments must be studied against a picture of severe forms of gut loss. Reports have shown that resections of the order of 75 per cent have been associated with high mortality and morbidity rates (Chen, 1969). A 75 per cent small bowel resection was therefore considered drastic enough to provide a suitable background against which the value of reversed segments could be assessed. The distal rather than proximal small bowel was removed to provide a rigorous challenge in terms of function and survival of the remnant. The ileocaecal valve was preserved to facilitate comparisons of glyceryl tri(palmitate-1-^{14}C) absorption and mouth-to-caecum transit time. Fat absorption is compromised by bacterial contamination from the colon and removal of the valve could have introduced this variable factor (Duret, 1972). Preservation of the ileocaecal valve and caecum further provided a clear end-point in radiological determinations of transit time.

Aspects of technique of segmental reversal have been discussed (Barros D'Sa, 1975a; Leading Article, 1975). A terminal reversed segment would allow maximal exploitation of the potential absorptive capacity of the remnant of bowel proximal to it. By contrast, a proximal segmental reversal may produce hyperacidity (Grundberg et al., 1967). The ideal length for reversal is considered to be within the range of 7·5–14 cm (Leading Article, 1975). Of clinical cases reported in the literature, 27 out of 31 reversed segments used were within the range of 7–15 cm and did not produce any significant complications (Barros D'Sa, 1975a). A third of the segments were 10 cm long, i.e. the length adopted in this study. The technique of Rygick and Nasarov (1969) was found to be impracticable when attempted in a pilot study using 10-cm segments (Barros D'Sa, 1975b). This is not surprising, as their technique utilized 20-cm lengths of bowel, which are excessive.

The control model was prepared in order to incorporate features which conceivably might account for the difference in results between the resection group and the reversal group. These were, first, the extra anastomosis of the reversal model and, secondly, transection of the terminal 10 cm of the remnant which in theory, produces a decreased frequency of the basic electrical rhythm in the isolated segment (Bass and Wiley, 1965).

Estimation of fat absorption after massive resection represents a sensitive index of alimentary function (Wapnick et al., 1969). Faecal fat estimations were open to several sources of error (Bergström and Blomstrand, 1956). As animal survival was being studied, fat absorption methods requiring serial blood sampling were avoided. As glyceryl tri-palmitate is the most common saturated fat in the average diet, glyceryl tri(palmitate-1-^{14}C) absorption by the breath analysis technique provided an adequate test of absorptive function in the experimental models prepared and shows significant correlation with faecal fat excretion (Burrows et al., 1974).

Hammer et al. (1959) first reported improvement in survival of dogs when massive resection was followed by reversing a 1-inch segment of small bowel. While a few other reports of short term beneficial results followed, some of these studies were performed using lengths of segment beyond the optimal range, and therefore not enough confidence can be placed in them (Singleton et al., 1961). Among the limited number of humans treated with reversed segments after resection, 2 patients had survived 7 and 7½ years respectively and were in excellent health (Hollender et al., 1972). In the present study the poor survival figures for the resection group are in keeping with the unsatisfactory results reported in other experimental series and in clinical reports of massive gut loss (Simons and Jordan, 1969). Survival time is clearly enhanced in the reversal group of animals.

Although some experimental workers, such as Repetto et al. (1965), showed that reversed segments diminished weight loss, other workers, including Delaney (1970), failed to observe such benefits. Keller et al. (1965) found that double reversed segments produced more rapid weight gain than when only one segment was used, but that long term survival was not obtained in the former group.

In this study, weight loss after resection was in keeping with observations in man. A review of the literature shows that those few patients who survive extensive resections remain at weight levels well below normal (Barros D'Sa, 1975b). Removal of the reversed segment in one healthy dog proved fatal and probably underlines the continued value of the reversed segment in sustaining life and suggests that adaptation of the remaining intestine is not an important factor in long term survival.

Absorption studies after experimental reversal showed transient improvement in one study using ^{131}I-labelled triolein (Singleton et al., 1961) and gave encouraging results in other studies employing faecal fat estimations (Venables et al., 1966; Depadt et al., 1970). From experiments with reversed segments and other surgical procedures, Delaney (1970) contested these results and stated that absorption was not ameliorated.

The method used in the present study permitted an 8-h quantitative measurement revealing the pattern of absorption. The preoperative peak of fat absorption at 7 h is not seen in subsequent studies in any of the three groups: this flattened curve is largely due to an impaired absorption, most marked in the resection group. It was suggested by Venables et al. (1966) that the prominent wave of peristalsis by the reversed segment permitted two periods of absorption, but such clear peaks were not observed. The consistent rise with time in fat absorption in the reversal group indicates that, regardless of loss of ileum and 75 per cent of bowel length, the remnant, with the aid of the reversed segment, was extremely successful in maintaining nutrition.

In this study transit time measurements excluded transit time through the colon to avoid inaccuracies, especially as dogs have a greater capacity than man for retaining faeces in the colon. Of all techniques for measuring intestinal transit, the radiological screening method afforded simple comparison of results and, of course, an opportunity to visualize the behaviour of the reversed segment.

The action of the reversed segment can best be explained on the basis of the local myenteric reflex (Bülbring, 1961). A schematic representation (*Fig.* 11) may assist in its understanding. A bolus of food entering a normal segment distends it, triggers the submucosal receptors to send an impulse backwards to the muscles which push the bolus forwards. A bolus entering a reversed segment also sends an impulse backwards, in this case distally because the segment is reversed and retains its polarity, thus causing the distal part of the reversed segment to contract and drive the food back up the remnant. Repeated contact of the meal with the mucosa in the remnant is permitted, thus allowing full use to be made of its limited absorptive potential.

The term 'physiological valve' used by Hammer et al. (1959) is inaccurate, and in his experiments using Thiry-Vella fistulas, Holstvgood (1971) confirmed

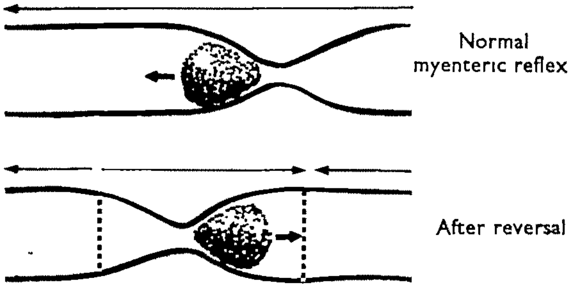


Fig. 11. Suggested mechanism of action of the reversed segment.

that there was no true valvular function. Recent experimental work has shown that levels of certain gastrointestinal hormones are altered not only by massive resection but also by segmental reversal, and this might explain some of the braking action of reversed segments (Barros D'Sa et al., 1975, 1976).

Reversal of the terminal segment of the remnant of jejunum after 75 per cent distal small bowel resection produces marked and progressive delay in intestinal transit time. This fits in well with sustained improvement in fat absorption, and, in turn, correlates well with weight status and enhanced survival. This contrasts markedly with both the resection and control groups which in all respects resemble each other. The possibility that either transection or the extra anastomosis necessary in fashioning a reversed segment may have been responsible for improvement in all parameters is therefore eliminated.

One question has to be raised. How much of the success of reversal can be ascribed to intestinal adaptation? While some adaptation might have occurred, general experience in animals and man shows that there is considerable individual variation in tolerance of massive resection and the capacity to adapt sufficiently to decrease morbidity and mortality. In the reversal group all animals showed significant and early improvement, while those in other groups universally exhibited relentless deterioration, and it is therefore unlikely that adaptation contributes significantly to the striking results, as illustrated by the outcome of removing the reversed segment in one healthy dog.

In conclusion, these studies demonstrate in greyhound dogs the beneficial effect of reversal of a 10-cm segment of bowel at the distal end of the remaining small intestine after the distal 75 per cent of the small bowel has been resected leaving the ileocaecal valve intact. It seems reasonable to apply these findings to the care of people who have severe intestinal insufficiency as a result of massive resection of small intestine.

Acknowledgements

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References

BARROS D'SA A. A. B. (1975a) Reversed loops in the short gut syndrome. *Br. Med. J.* 3, 543.

BARROS D'SA A. A. B. (1975b) Pathophysiological aspects of massive small bowel resection with an assessment of the functional value of reversed segments. MD(Hons) Thesis, The Queen's University of Belfast.

BARROS D'SA A. A. B. (1979) The pill, mesenteric vein thrombosis and the short, short bowel syndrome. *Br. J. Clin. Pract.* (In the press.)

BARROS D'SA A. A. B. and BUCHANAN K. D. (1977) Role of gastrointestinal hormones in the response to massive resection of the small bowel. *Gut* 18, 877–881.

BARROS D'SA A. A. B., KENNEDY T. L., BUCHANAN K. D. et al. (1975) Gastrointestinal hormonal responses following massive small bowel resection. *Br. J. Surg* 62, 152.

BARROS D'SA A. A. B., PARKS T. G., KENNEDY T. L. et al. (1976) Hormonal alterations caused by segmental reversal after massive small bowel resection. *Eur. Surg. Res.* 8, Suppl. pp. 3–4.

BARROS D'SA A. A. B., PARKS T. G. and ROY A. D. (1978) The problems of massive small bowel resection and difficulties encountered in management. *Postgrad. Med. J.* 54, 323–328.

BASS P. and WILEY J. N. (1965) Electrical and extraluminal contractile-force activity of the duodenum of the dog. *Am. J. Dig. Dis.* 10, 183–200.

BERGSTROM S. and BLOMSTRAND R. (1956) In: POPJACK G. and LE BRETON E. (ed.) *Biochemical Properties of Lipids.* London, p. 323.

BLADES J. F. and PEPLE W. L. (1976) Treatment of the short intestinal syndrome by the reverse loop method. *Virginia Med. Mth* 97, 360–361.

BUDDING J. and SMITH C. G. (1967) Role of recirculating loops in the management of massive resection of the small intestine. *Surg. Gynecol. Obstet.* 125, 243–249.

BÜLBRING E. (1961) Motility of the intestine. *Proc. R. Soc. Med.* 54, Suppl. pp. 773–775.

BURROWS D. J., FLEMING J. S., GARNETT E. S. et al. (1974) Clinical evaluation of the ^{14}C fat absorption test. *Gut* 15, 147–150.

BURROWS L., WILDSTEIN W., DREILING D. A. et al. (1965) Effects of anti-peristaltic ileal segment on bowel function. *Surgery* 58, 999–1005.

CHEN KAI-MO (1969) Massive resection of the small intestine. *Surgery* 65, 931–938.

COLCOCK B. P. and BRAASCH J. W. (1968) Small intestinal insufficiency. In: *Surgery of the Small Intestine in the Adult.* Philadelphia, Saunders, pp. 116–129. (*Major Problems in Clinical Surgery*, vol. VII.)

CRAFT I. L. and VENABLES C. W (1968) Antiperistaltic segment of jejunum for persistent diarrhoea following vagotomy. *Ann. Surg.* 167. 282–286.

DELANEY H. M. (1970) Experimental massive intestinal resection. Comparison of surgical measures and spontaneous adaptation. *Arch. Surg* 101, 599–604.

DEPADT G., LAURENT J.-C. and LAGACHE G. (1970) Surgical problems of massive resections of the small intestine. Experimental study. *Ann. Chir.* 24, 571–575.

DURET R. L. (1972) Glucid absorption after massive small intestinal reversal. *Acta Gastroenterol Belg.* 35, 172–180.

ELLIS H. and COLL I. (1968) Antiperistaltic segment for profuse ileostomy diarrhoea. *Br. Med. J* 1, 556–557.

FINK W. J. and OLSON J. D. (1967) The massive bowel resection syndrome. Treatment with reversed intestinal segments. *Arch. Surg.* 94, 700–706.

GIBSON D. L., CARTER R. and HINSHAW D. B. (1962) Segmental reversal of small intestine after massive small bowel resection. Successful case with follow-up examination. *JAMA* 182, 952–954.

GRUNDBERG A. B., LOPEZ A. S and DRAGSTEDT L. R. (1967) Effect of intestinal reversal and massive resection on gastric secretion. *Arch. Surg.* 94, 326–329.

HAMMER J. M., SEAY P. H., JOHNSON R. L. et al. (1959) The effect of antiperistaltic bowel segments on intestinal emptying time. *Arch. Surg.* 79, 537–541.

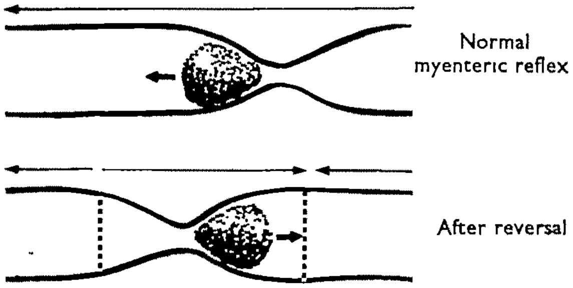

Fig. 11. Suggested mechanism of action of the reversed segment.

that there was no true valvular function. Recent experimental work has shown that levels of certain gastrointestinal hormones are altered not only by massive resection but also by segmental reversal, and this might explain some of the braking action of reversed segments (Barros D'Sa et al., 1975, 1976).

Reversal of the terminal segment of the remnant of jejunum after 75 per cent distal small bowel resection produces marked and progressive delay in intestinal transit time. This fits in well with sustained improvement in fat absorption, and, in turn, correlates well with weight status and enhanced survival. This contrasts markedly with both the resection and control groups which in all respects resemble each other. The possibility that either transection or the extra anastomosis necessary in fashioning a reversed segment may have been responsible for improvement in all parameters is therefore eliminated.

One question has to be raised. How much of the success of reversal can be ascribed to intestinal adaptation? While some adaptation might have occurred, general experience in animals and man shows that there is considerable individual variation in tolerance of massive resection and the capacity to adapt sufficiently to decrease morbidity and mortality. In the reversal group all animals showed significant and early improvement, while those in other groups universally exhibited relentless deterioration, and it is therefore unlikely that adaptation contributes significantly to the striking results, as illustrated by the outcome of removing the reversed segment in one healthy dog.

In conclusion, these studies demonstrate in greyhound dogs the beneficial effect of reversal of a 10-cm segment of bowel at the distal end of the remaining small intestine after the distal 75 per cent of the small bowel has been resected leaving the ileocaecal valve intact. It seems reasonable to apply these findings to the care of people who have severe intestinal insufficiency as a result of massive resection of small intestine.

Acknowledgements

I am indebted to the Royal Victoria Hospital, Belfast, for a Research Fellowship which has made it possible to undertake this work. My thanks are due to Mr T. L. Kennedy, Professor A. D. Roy, Mr T. G. Parks and Professor A. H. G. Love for their advice, interest and helpful discussions; to the technical staff of the Department of Surgery; to Mr J. Todd for assistance with radioisotopes; to Mr George Smith for the illustrations; to Mrs Liz Thompson for the graphs; and to Miss May Weller for her continued help and expertise in preparing this manuscript.

References

BARROS D'SA A. A. B. (1975a) Reversed loops in the short gut syndrome. *Br. Med. J.* 3, 543.

BARROS D'SA A. A. B. (1975b) Pathophysiological aspects of massive small bowel resection with an assessment of the functional value of reversed segments. MD(Hons) Thesis, The Queen's University of Belfast.

BARROS D'SA A. A. B. (1979) The pill, mesenteric vein thrombosis and the short, short bowel syndrome. *Br. J. Clin. Pract.* (In the press.)

BARROS D'SA A. A. B. and BUCHANAN K. D. (1977) Role of gastrointestinal hormones in the response to massive resection of the small bowel. *Gut* 18, 877–881.

BARROS D'SA A. A. B., KENNEDY T. L., BUCHANAN K. D. et al. (1975) Gastrointestinal hormonal responses following massive small bowel resection. *Br. J. Surg* 62, 152.

BARROS D'SA A. A. B., PARKS T. G., KENNEDY T. L. et al. (1976) Hormonal alterations caused by segmental reversal after massive small bowel resection. *Eur. Surg. Res.* 8, Suppl. pp. 3–4.

BARROS D'SA A. A. B., PARKS T. G. and ROY A. D. (1978) The problems of massive small bowel resection and difficulties encountered in management. *Postgrad. Med. J.* 54, 323–328.

BASS P. and WILEY J. N. (1965) Electrical and extraluminal contractile-force activity of the duodenum of the dog. *Am. J. Dig. Dis.* 10, 183–200.

BERGSTROM S. and BLOMSTRAND R. (1956) In: POPJACK G. and LE BRETON E. (ed.) *Biochemical Properties of Lipids.* London, p. 323.

BLADES J. F. and PEPLE W. L. (1976) Treatment of the short intestinal syndrome by the reverse loop method. *Virginia Med. Mth* 97, 360–361.

BUDDING J. and SMITH C. G. (1967) Role of recirculating loops in the management of massive resection of the small intestine. *Surg. Gynecol. Obstet.* 125, 243–249.

BÜLBRING E. (1961) Motility of the intestine. *Proc. R. Soc. Med.* 54, Suppl. pp. 773–775.

BURROWS D. J., FLEMING J. S., GARNETT E. S. et al. (1974) Clinical evaluation of the ^{14}C fat absorption test. *Gut* 15, 147–150.

BURROWS L., WILDSTEIN W., DREILING D. A. et al. (1965) Effects of anti-peristaltic ileal segment on bowel function. *Surgery* 58, 999–1005.

CHEN KAI-MO (1969) Massive resection of the small intestine. *Surgery* 65, 931–938.

COLCOCK B. P. and BRAASCH J. W. (1968) Small intestinal insufficiency. In: *Surgery of the Small Intestine in the Adult.* Philadelphia, Saunders, pp. 116–129. (*Major Problems in Clinical Surgery*, vol. VII.)

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DELANEY H. M. (1970) Experimental massive intestinal resection. Comparison of surgical measures and spontaneous adaptation. *Arch. Surg* 101, 599–604.

DEPADT G., LAURENT J.-C. and LAGACHE G. (1970) Surgical problems of massive resections of the small intestine. Experimental study. *Ann. Chir.* 24, 571–575.

DURET R. L. (1972) Glucid absorption after massive small intestinal reversal. *Acta Gastroenterol Belg.* 35, 172–180.

ELLIS H. and COLL I. (1968) Antiperistaltic segment for profuse ileostomy diarrhoea. *Br. Med. J* 1, 556–557.

FINK W. J. and OLSON J. D. (1967) The massive bowel resection syndrome. Treatment with reversed intestinal segments. *Arch. Surg.* 94, 700–706.

GIBSON D. L., CARTER R. and HINSHAW D. B. (1962) Segmental reversal of small intestine after massive small bowel resection. Successful case with follow-up examination. *JAMA* 182, 952–954.

GRUNDBERG A. B., LOPEZ A. S and DRAGSTEDT L. R. (1967) Effect of intestinal reversal and massive resection on gastric secretion. *Arch. Surg.* 94, 326–329.

HAMMER J. M., SEAY P. H., JOHNSON R. L. et al. (1959) The effect of antiperistaltic bowel segments on intestinal emptying time. *Arch. Surg.* 79, 537–541.

Br. J. Surg. Vol. 66 (1979) 501–504

Use of circular stapling gun with peranal insertion of anorectal purse-string suture for construction of very low colorectal or colo-anal anastomoses

J. C. GOLIGHER*

SUMMARY

A technique is described for construction of the colorectal or colo-anal anastomosis in low rectal resection by using an automatic circular stapling device and inserting the anorectal purse-string suture peranally from below. This method was employed in 4 patients resulting in complete healing in 3 cases and a moderate leak in 1, which, however, eventually healed satisfactorily.

We have described our initial encouraging experiences with the new Russian circular stapling gun for the construction of colorectal anastomoses in anterior resection (Goligher et al., 1979). One of the advantages of this device is that an anastomosis can be achieved at a lower level than would be feasible with hand-placed sutures. Thus it has been possible with its aid to extend the range of anterior resection. A sphincter-saving resection by abdomino-anal pullthrough, abdomino-transanal, abdomino-sacral or abdomino-transsphincteric techniques has still to be considered for lower carcinomas of the middle third of the colon.

These different operative methods have their respective advantages and disadvantages and the choice between them is a very personal one for the individual surgeon. Currently the abdomino-transanal technique of Parks (1972) is attracting a good deal of attention in Britain. It involves a very low resection from the abdominal aspect, leaving a small anorectal remnant comprising little more than the anal canal. Continuity of the intestinal tract is restored by a sutured anastomosis between the colon stump and the anorectal remnant, conducted from below through the anus opened up by a bivalve anal retractor. For this purpose Parks (1972) originally used a single row of interrupted end-to-end sutures between the cut lower edge of the colon stump and the cut upper edge of the anorectal stump, just at or immediately above or below the anorectal ring. More recently, however (Parks and Thomson, 1977), Parks has favoured a technique which provides for 'coring out' the mucosa of the anorectal remnant from the underlying internal sphincter and circular muscle coat, starting 0·5–1·0 cm above the pectinate line and working up to the top edge of the remnant. The colon stump is then drawn down through the denuded anal canal. It is fixed by a few sutures passed between its serosal surface and the upper edge of the muscle coat of the anorectal remnant, and then its cut lower edge is sutured to the anal mucosa just above the pectinate line by a circumferential series of interrupted 2/0 Dexon sutures that also include some of the internal sphincter in their bite. Parks and Thomson (1977) believe that this type of imbricated or sleeve anastomosis is more secure than an ordinary end-to-end suture.

Recently the present author has found that the construction of a simple end-to-end colo-anal or colorectal anastomosis in abdomino-transanal resection can be greatly facilitated by using the circular stapling gun in the same way as it is employed in anterior resection, except that the purse-string suture in the top of the anorectal stump is inserted not from the abdominal aspect, but from below through the anal canal held open by a bivalve speculum.

Technique

The operation is conducted with the patient in the lithotomy-Trendelenburg position (Lloyd-Davies, 1939), which gives simultaneous access to the abdomen and anal region. The carcinomatous segment of rectum and most of the sigmoid are resected in the usual way, a distal margin of clearance of 4–5 cm being secured. Both the rectal and colonic stumps are controlled by crushing Parker–Kerr clamps. In due course these will be removed by excising them from the bowel; purse-string sutures will then be inserted in the ends of both stumps. However, it is best to leave the clamp on the colon stump till the purse-string has been placed in the rectal stump, otherwise troublesome faecal leakage from the colon may take place whilst the latter manoeuvre is being carried out.

Insertion of purse-string suture in superior edge of anorectal stump per anum

A bivalve speculum capable of wide separation of its blades, such as the larger version of the author's own retractor (made by C. F. Thackray, Park Street, Leeds) or of Parks's retractor, is introduced into the anal canal and opened to its fullest extent. The third blade is then inserted to improve the access still further. By this means a good view is obtained of the interior of the posterior wall of the anorectal remnant up to its superior edge. The purse-string suture of 2/0 monofilament Prolene or well-waxed fine linen thread, which is going to be placed along the upper edge, is started in the midline posteriorly, being passed from the mucosal aspect outwards through the rectal wall about 4 mm from the cut edge (*Fig.* 1). The stitch is continued to the patient's right with a series of similar bites of the needle from within outwards at intervals of 4 mm along the top of the anorectal stump and 4 mm from the cut edge. When the right margin of the exposed sector of anorectal wall is reached, the retractor is rotated in a clockwise direction through 90 degrees and the stitch is continued along the top edge of that sector. By further rotations in due course the anterior and left lateral sectors are similarly exposed for suture, till finally the posterior sector is again exposed and the suture reaches its starting point (*Fig.* 1). The suture is not at this stage tightened or tied, but the ends are left long and emerge through the anus.

Introduction of suture gun and tying of anorectal purse-string suture on central shaft

There are two ways in which the purse-string suture thus inserted into the top of the anorectal stump can be tied on the central shaft of the suture gun. By one method it is done entirely from below. The third blade of the retractor is now removed and the amount of separation of the other two blades slightly reduced. The suture gun is then lubricated, opened to the maximum extent and introduced through the anal canal into the pelvis, sufficiently far to take the head end above the upper edge of the anorectal stump, whilst the central shaft lies in the anal canal itself and the shoulder-piece is still below the anal verge (*Fig.* 2). The anal retractor is next withdrawn

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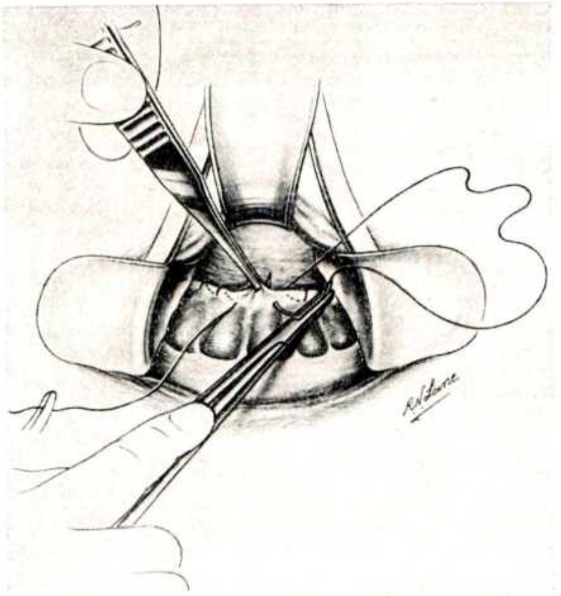

Fig. 1. View obtained of interior of anorectal remnant with anal speculum in position. The 2/0 monofilament Prolene suture has been inserted along the top of the remnant starting in the midline posteriorly and continuing as an over-and-over stitch from inside the lumen 4 mm or so from the cut edge, the retractor having been rotated to expose each sector of the bowel in turn. The stitch has now reached the posterior sector again and is approaching the starting point.

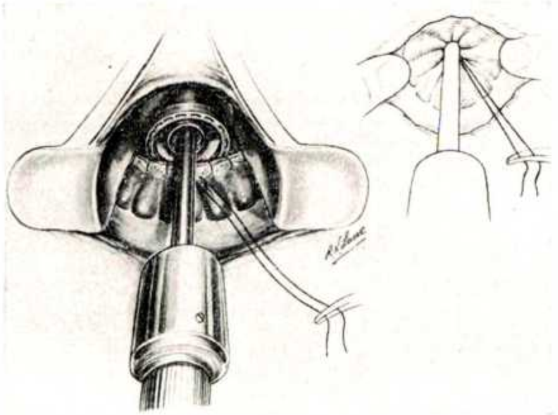

Fig. 2. The third blade of the anal retractor has been removed and the separation of the other two blades reduced somewhat, whilst the head end of the opened suture gun is inserted through the anal canal to beyond the top of the anorectal remnant. (Inset) The anal retractor has been removed and the anorectal purse-string suture has been tied from below on the central shaft.

completely and the tails of the purse-string suture on the top of the anorectal stump are tied firmly on the central shaft, the knotting being assisted by the points of the two index figures being passed up inside the anal canal (*Fig.* 2 inset).

The alternative, and usually preferable, way of tying the anorectal purse-string suture is to do so from above. In this technique the tails of the loosely placed suture which project through the anus are clipped at their ends with a long artery forceps and passed up through the anal canal to be grasped by the abdominal operator using a similar pair of long forceps passed down into the pelvis. The perineal operator releases his

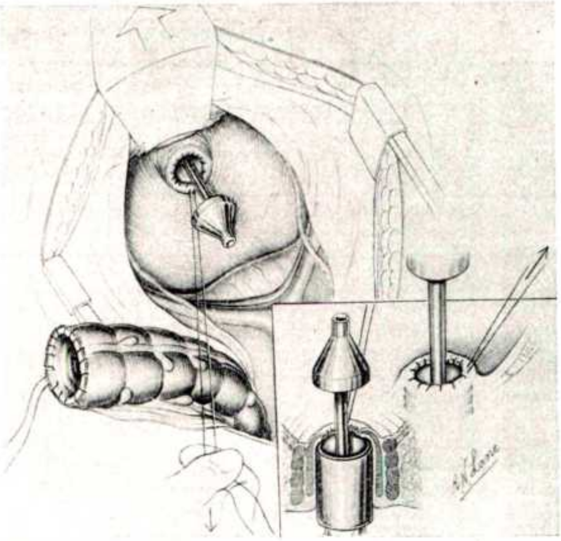

Fig. 3. Alternative method of tying anorectal purse-string suture from above. The tails of the suture have been passed up through the anal canal to the abdominal operator. Whilst the bladder and prostate are retracted strongly forwards to expose the top of the anorectal remnant held up by the purse-string suture, the suture gun is inserted from below by an assistant and opened to carry the head into the pelvis beyond the edge of the anorectal stump, whilst the distal edge of the shoulder-piece still lies in the remnant (*see* inset). The purse-string suture is then tied on the central shaft just above the shoulder-piece.

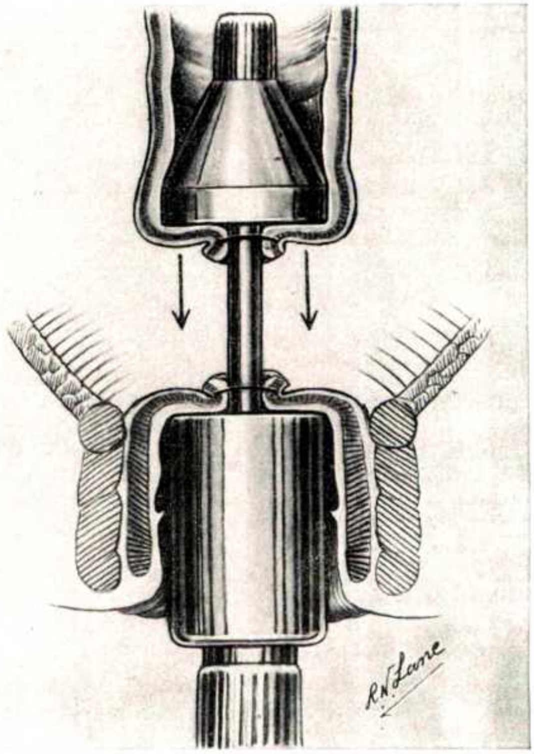

Fig. 4. Diagrammatic view of the 'opened' suture gun in position with the purse-string sutures in both anorectal and colonic stumps tied and the instrument about to be 'closed' preparatory to 'firing' the staples.

hold on the suture, the tails of which are then drawn up into the abdominal field. The bladder, seminal vesicles and prostate (or uterus and vagina) are now retracted strongly forwards by the abdominal operator to display the top of the anorectal remnant held up by traction on the ends of its purse-string suture (*Fig*. 3). The perineal assistant has meanwhile removed the bivalve anal speculum and introduced the lubricated closed suture gun into the anal canal. As soon as the tip of the conical head is seen emerging through the top of the stump by the abdominal surgeon, the gun is 'opened' by the perineal operator to advance the head-piece into the pelvis 4–5 cm beyond the cut edge of the anorectal remnant, whilst the shoulder-piece is still in the anal canal just below the purse-string suture (*Fig*. 3. inset). The suture is then tied firmly on the central shaft immediately above the shoulder-piece.

Advancement of gun in anal canal and fastening of colon stump

With the first method of tying the anorectal purse-string suture from below, the shoulder-piece of the gun does not at this stage lie properly in the anal canal. Accordingly the gun is now advanced gently so that the edge of the shoulder-piece proceeds up the anorectal remnant as far as the purse-string suture on its upper end will allow. With the second method of tying the anorectal purse-string suture from above the shoulder-piece is already in this position (*Fig*. 4). The abdominal surgeon then takes the end of the colon stump, into which a purse-string suture of 2/0 monofilament Prolene has already been loosely inserted, and slips it over the conical head of the gun, the purse-string suture being immediately tied on the central shaft to hold the bowel in place (*Fig*. 4).

Closing and 'firing' of gun

By clockwise rotation of the wheel on the proximal end of the barrel of the gun the head and shoulder-pieces are gradually opposed till the gap between these two parts is reduced to 1·5–2·0 mm. The gun is then 'fired' by approximating the two limbs of the handle with a sudden sharp movement, the effect being to drive the staples through the compressed tissues of the colonic and rectal walls and at the same time to cut through these walls with the circular trephine knife just internal to the staple line.

Extraction of gun

By winding the wheel in an anticlockwise direction the head and shoulder-piece are separated sufficiently to release the stapled flange of bowel wall and the instrument is gently extricated from the bowel, leaving a colorectal or coloanal anastomosis at or just above the anorectal ring (*Fig*. 5).

Results

So far this technique of inserting the anorectal purse-string suture from below through the anal canal has been employed in only 4 patients. All were men and all had rectal carcinomas at 8·0, 8·0, 8·5 and 9·0 cm respectively from the anal verge on preoperative sigmoidoscopic examination; 2 of the men were decidedly obese. The placing and tying of the anorectal purse-string suture was certainly easier than inserting sutures directly between the colonic and anorectal stump by either of the techniques described by Parks (1972) and Parks and Thomson (1977). Radiological studies after Gastrografin enemas, as described in previous publications (Goligher, Graham et al., 1970; Goligher, Morris et al., 1970; Goligher et al., 1977) were conducted on all 4 patients, but the opaque medium was injected not per anus as an enema for fear of injuring the anastomotic line with the rectal tube, but through the distal opening of the covering transverse colostomy that was established in all these cases. In one case a moderate anastomotic dehiscence was revealed but it subsequently healed satisfactorily and the patient did well. In all the other cases the anastomoses were intact. The sigmoidoscopic heights of the anastomoses were 5·0, 4·5 (2 cases) and 4·0 cm.

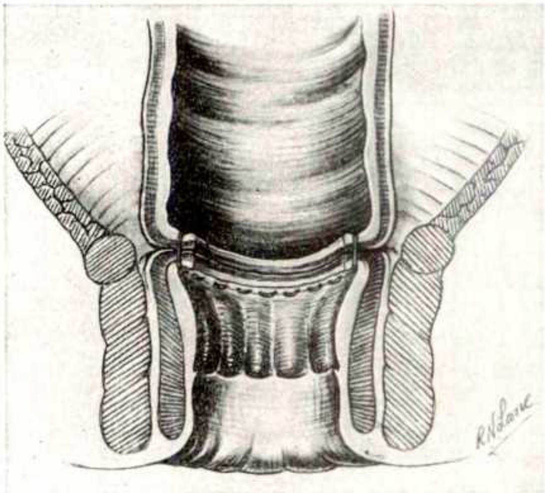

Fig. 5. A diagrammatic representation of the stapled anastomosis at or just above the anorectal ring after withdrawal of the gun.

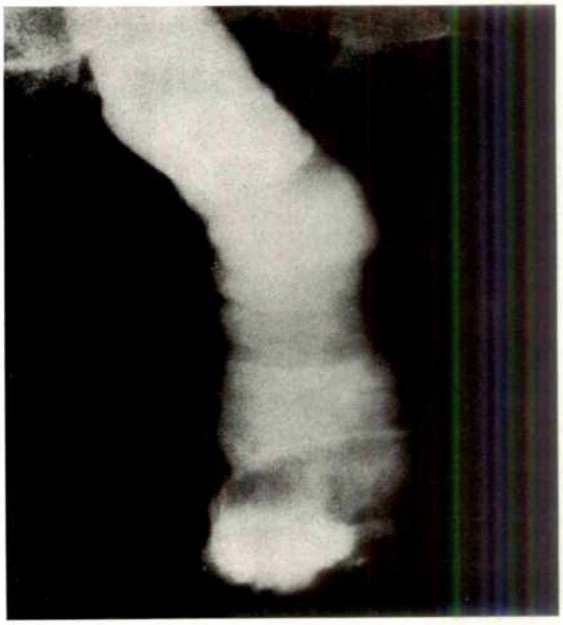

Fig. 6. Radiological examination after Gastrografin enema in a man treated by abdomino-transanal resection using the circular stapling gun for construction of the anastomosis. The staples indicate the site of the very low anastomosis, which is intact, just above the anorectal ring.

In 3 patients the covering transverse colostomy was closed after 2 months. When the faecal flow was at first restored to the anal canal there was a greatly increased frequency of defaecation with as many as 12–15 calls to stool per day and a good deal of incontinence for flatus and faeces. Gradually the frequency became less and the control better, and 2 of the 3 patients are now fully continent 5 and 7 months after closure of the colostomy but still have bowel actions at least 4–7 times daily. The third patient, who had his colostomy closed 3 months ago, is still not completely continent but his function is improving. The fourth patient, whose operation was performed only 6 weeks ago, still retains his colostomy.

References

GOLIGHER J. C., GRAHAM N. G. and DE DOMBAL F. T. (1970) Anastomotic dehiscence after anterior resection of the rectum and sigmoid. *Br. J. Surg.* **57**, 109–118.

GOLIGHER J. C., LEE P. W. R., MACFIE J. et al. (1979) Experiences with the Russian model 249 suture gun in the construction of rectal anastomoses. *Surg. Gynecol. Obstet.* **148**, 517.

GOLIGHER J. G., LEE P. W. R., SIMPKINS K. C. et al. (1977) A controlled comparison of one- and two-layer techniques of suture for high and low colorectal anastomoses. *Br. J. Surg.* **64**, 609–614.

GOLIGHER J. C., MORRIS C., MCADAM W. A. F. et al. (1970) A controlled trial of inverting versus everting intestinal suture in clinical large bowel surgery. *Br. J. Surg.* **57**, 817–822.

LLOYD-DAVIES I. V. (1939) Lithotomy–Trendelenburg position for resection of rectum and lower pelvic colon. *Lancet* **2**, 74–76.

PARKS A. G. (1972) Transanal technique in low rectal anastomoses. *Proc. R. Soc. Med.* **64**, 975–976.

PARKS A. G. and THOMSON J. P. S. (1977) Peranal endorectal operative techniques. In: TODD I. P. (ed.) *Colon, Rectum and Anus.* London, Butterworths, p. 157 (*Operative Surgery*, 3rd ed.).

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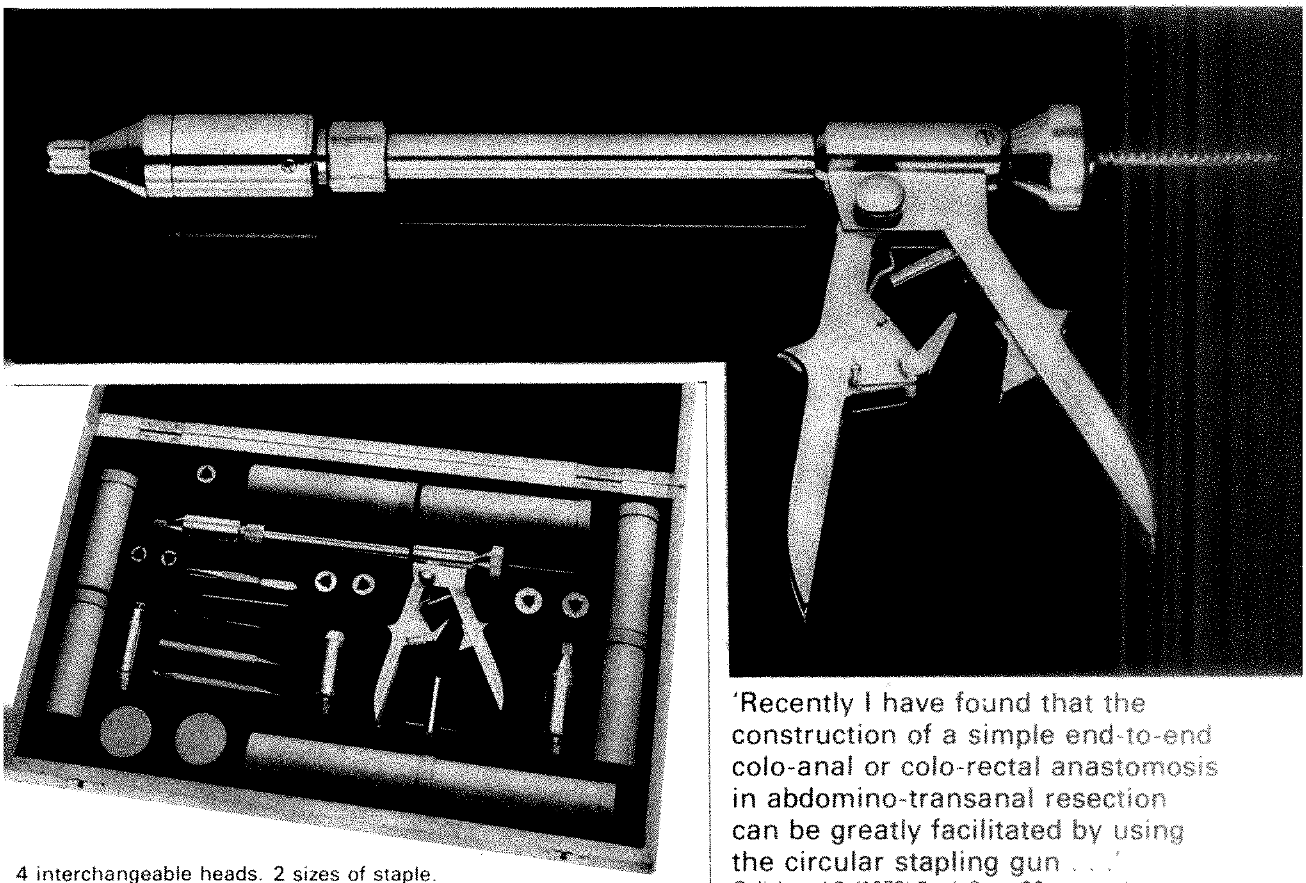

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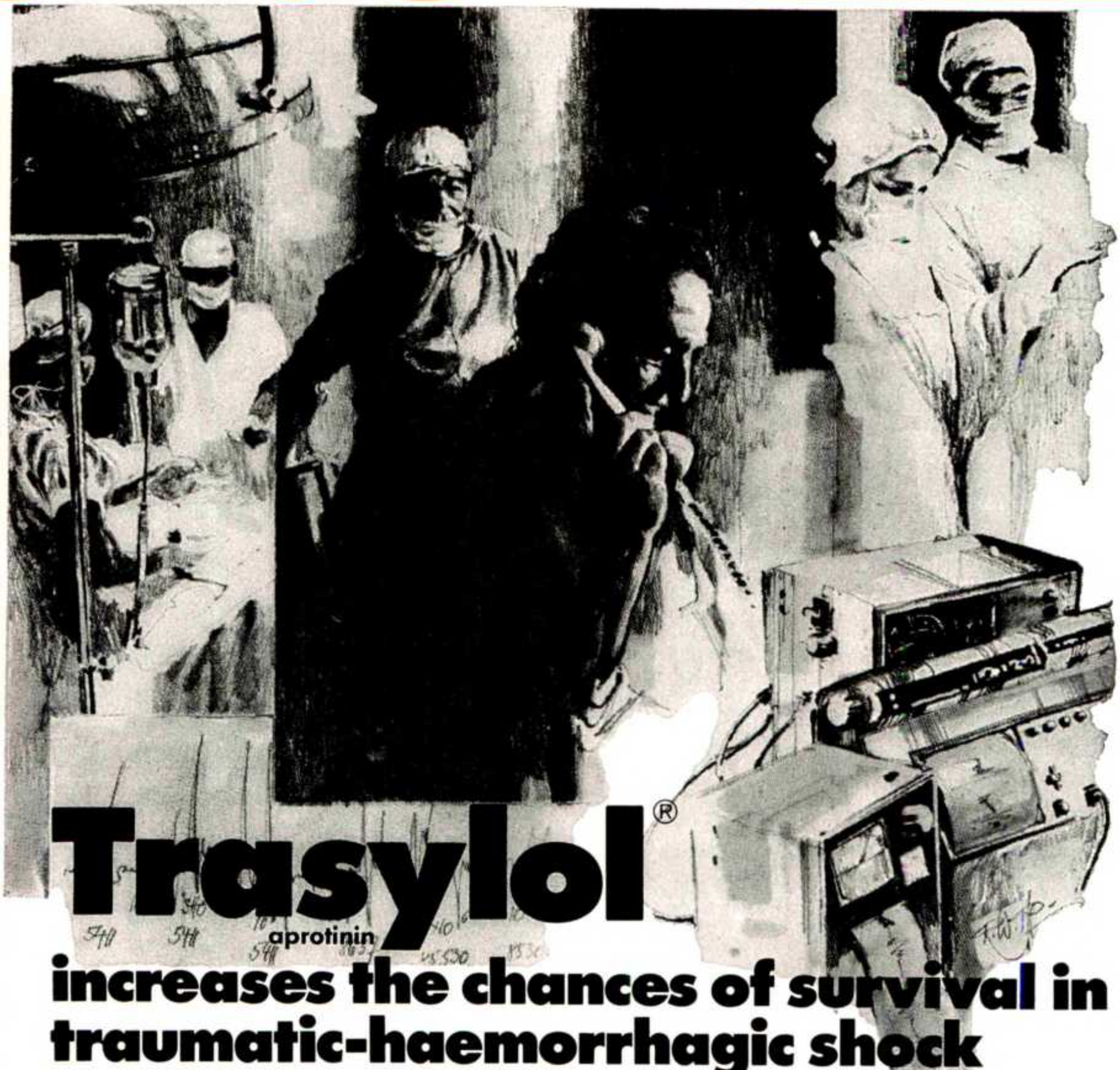

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2) McMichan et al., Med. Welt **27,** 2331 (1976)

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Transcutaneous defunctioning colostomy

FERNANDO REÑAGA SYKES*

SUMMARY

The technique is described for constructing an occlusive tube colostomy which requires no second operative procedure for closure. The advantages of this method are discussed and it is recommended as a superior alternative to loop colostomy or caecostomy for defunctioning the unobstructed distal bowel.

DIVERSION of the faecal stream to defunction the distal colon presents technical problems; the two most important are, that the diversion of the faecal stream is frequently incomplete and that a second operation is required to close the colostomy. The aim of this paper is to describe a technique which overcomes these problems.

Method

The part of the colon selected for the colostomy is brought out through the omentum so that the omentum shields the remaining abdominal cavity from faecal contamination. A soft Penrose drain 2–3 cm wide and 20 cm long is passed through the mesocolon near the bowel wall. Three centimetres proximal to the Penrose drain and on the antimesenteric border of the colon, preferably through a taenia coli, a longitudinal incision 2 cm long is made. A de Pezzer catheter, with the side holes enlarged, is passed into the lumen of the bowel through the incision (*Fig.* 1). A purse-string suture is placed around the catheter to avoid spillage. The de Pezzer catheter is invaginated into the wall of the colon by suturing the serosa over the catheter for a distance of 8–10 cm. Two skin incisions 3 cm long are made parallel to the colon at the site of the Penrose drain, each end of which is brought out through an incision. A third incision is made for the de Pezzer catheter, between those for the Penrose drain and the laparotomy wound (*Fig.* 2).

The ends of the Penrose drain are tied over a gauze swab, ensuring that the lumen of the colon is occluded against the abdominal wall without impairing the blood supply. The tip of the de Pezzer catheter now lies free in the proximal colon with the distal end occluded by the Penrose drain. Having ascertained that the de Pezzer catheter is suitably sited, it is sutured to the abdominal wall.

On completion of the transcutaneous defunctioning colostomy, the laparotomy incision is closed. Anal dilatation is a routine procedure following this operation.

Postoperatively the catheter is attached to tubing, and washouts through the catheter are only performed if there is a suspicion of tube blockage. In order to remove the tube, which is left in place for a minimum of 3 weeks, one end of the Penrose drain is divided (*Fig.* 3) and the drain is withdrawn. The de Pezzer tube is then removed and normal gastrointestinal continuity restored without a further operative procedure. Barium enema studies performed after removal of the drain show a narrowing at the site of the colostomy; however, a repeat examination at 1 year shows a normal colonic lumen.

Discussion

To date, 12 transcutaneous defunctioning colostomies have been performed (low rectal anastomosis, 10; traumatic faecal fistula in the sigmoid, 1; sigmoid myotomy, 1). The only complication in this series occurred in the first patient whose catheter was removed on day 14 after operation; this resulted in leakage along the catheter track causing an abscess. This was aggravated by the passage of the catheter through the upper end of the laparotomy wound. For

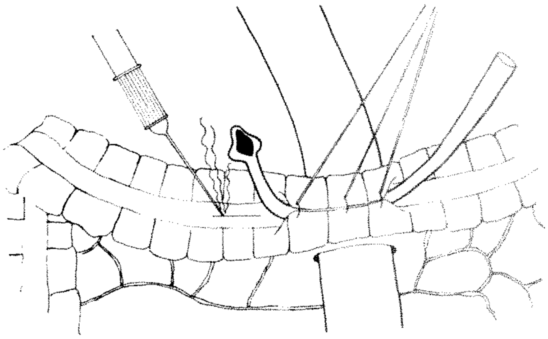

Fig. 1. The Penrose drain has been placed through the mesentery and the incision in the taenia coli of the antimesenteric border is being made. Note the enlarged opening in the tip of the de Pezzer catheter.

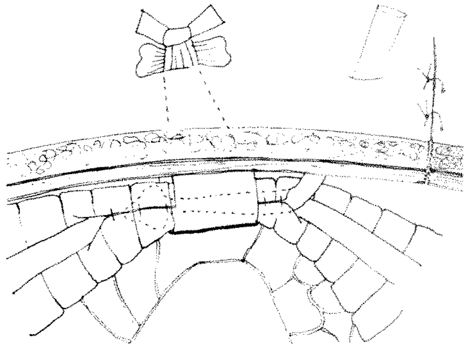

Fig. 2. The completed operation. The Penrose drain has been tied over a gauze swab, and the tube drain brought out through a separate incision between the Penrose drain and the abdominal wound.

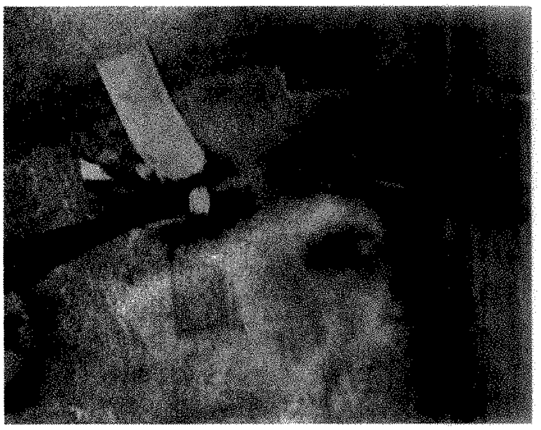

Fig. 3. Removal of the transcutaneous colostomy: the Penrose drain is being divided on the skin surface in preparation for removal.

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this reason a separate incision was made in the remaining cases.

The indications for this procedure are indentical to those of the usual loop colostomy, but in the presence of complete obstruction distal to the colostomy, the dangers associated with a closed loop would occur. Even in the presence of partial obstruction, this colostomy would not enable complete clearance of the faecal contents of the bowel immediately proximal to the obstruction, hence, it would not be advised in the management of obstruction.

However, the place of this procedure is in those instances when complete rest of the distal colon is required, such as in the presence of a faecal fistula. For defunctioning the colon in order to protect an anastomosis it is ideal, producing a complete exclusion, yet not requiring a second operation to clear the colostomy. Because the faeces drain through a tube into a bag, the patient is spared the discomfort of a colostomy, which, particularly in the immediate postoperative period, is hard to manage. The emotional stress to which many patients are submitted by the appearance of a colostomy is avoided by this technique and the inevitable odour is reduced by the closed drainage technique described.

The technique of transcutaneous defunctioning colostomy is proposed as an alternative to both loop colostomy and a caecostomy, overcoming the disadvantages of both techniques and having few, if any, drawbacks of its own.

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Pyloromyotomy forceps

A. G. JOHNSON AND F. KHAN*

A NUMBER of different instruments have been devised for performing pyloromyotomy (Ramstedt's operation) in infants (Quinby, 1966; Benson, 1969). The best known is the Dennis Browne forceps (Browne, 1951), but this is only useful at the end of the operation when the muscle has been well separated, because its tips are 3 mm apart when closed. Many surgeons insert a small curved haemostat into the scalpel incision to separate the circular muscle fibres, but this is often too wide and is smooth on the outside and tends to slip. The new forceps (GU Manufacturing Co. Ltd, Plympton Street, London) illustrated in *Fig.* 1 is serrated on the *outside* and closes to form a sharp 'keel' (*inset*) which can be inserted into the initial scalpel incision. The curve of the blades follows the shape of the pyloric muscle in longitudinal section and the tip is blunt so as not to damage the thin fornix of the duodenal wall at the end of the incision. For the past 3 years the forceps has been found useful by more experienced surgeons as well as by registrars learning the operation for the first time.

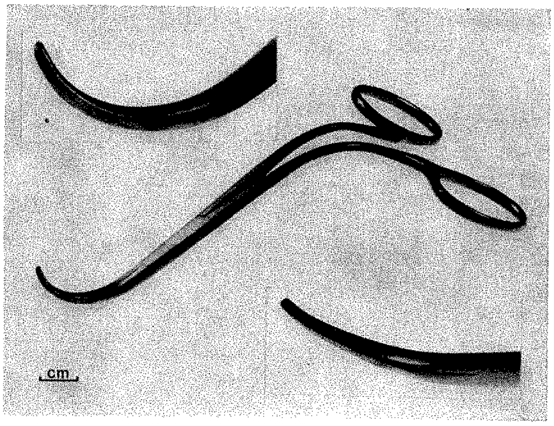

Fig. 1. The forceps, with close-up views of the tips.

References

BENSON C. D. (1969) Prepyloric and pyloric obstruction. In: MUSTARD W. T., RAVITCH M. M., SNYDER W. H. et al. (ed.) *Paediatric Surgery*. Chicago, Year Book, vol. 2, p. 795.

BROWNE D. (1951) The technique of Ramstedt's operation. *Proc. R. Soc. Med.* **44**, 1057–1059.

QUINBY W. C. (1966) Complete pyloromyotomy without duodenal perforation. *Surgery* **59**, 627–630.

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The effect of levamisole on postoperative immunosuppression

R. WINDLE, R. F. M. WOOD AND P. R. F. BELL*

SUMMARY

Cell mediated immunity was studied before and after surgery in patients with colorectal cancer. Thymus-derived (T) lymphocytes were enumerated and their non-specific activity was measured by assessing phytohaemagglutinin (PHA)-induced blastogenesis. Specific T lymphocyte activity was measured by leucocyte migration inhibition in response to purified protein derivative of tuberculin (PPD) and autochthonous tumour extract. One group of patients received levamisole postoperatively and the other group consisted of controls. There was a more rapid return to preoperative levels of leucocyte migration inhibition to both antigens by the levamisole group. However, levamisole administration had only a marginal effect on the postoperative depression of cell counts and did not restore depressed lymphoblast transformation.

FOLLOWING surgery there is a depression of cell mediated immunity. This has been demonstrated by a reduction in the numbers of circulating thymus-derived (T) lymphocytes (Miller et al., 1976). In addition, lymphoblast transformation in response to phytohaemagglutinin (PHA) (Riddle and Berenbaum, 1967; Park et al., 1971) and leucocyte migration inhibition (Cochran et al., 1972) are both depressed after operation.

Intraoperative manipulation of a malignant lesion may cause dissemination of cells. A reduction in cell mediated immunity at such a time could therefore detrimentally affect prognosis.

Levamisole, an anthelmintic agent, has been shown to restore cell mediated immunity depressed by age (Verhaegen et al., 1973) or cancer (Tripodi et al., 1973). The effect of levamisole on cell mediated immunity depressed following surgery has not to our knowledge been reported.

We have investigated cell mediated immunity before and after surgery for colorectal cancer and have assessed the effect of the postoperative administration of levamisole.

Cell mediated immunity was studied using three techniques:

1. Enumeration of T lymphocytes.
2. The leucocyte migration inhibition test in response to purified protein derivative of tuberculin (PPD) and autochthonous tumour.
3. The degree of blastogenesis in response to phytohaemagglutinin (PHA).

Patients and methods

Two groups of 10 patients with colorectal cancer were studied. One group of patients received 50 mg of levamisole three times per day orally on the first 3 postoperative days. The other group of patients acted as controls and were not given levamisole. The groups were age-matched with 8 males and 2 females in each group. In 7 patients in each group the tumour was confined to the bowel and a curative resection was performed. Three patients in each group had extensive disease with lymph node involvement or distant metastases. Of these 6 patients, 4 had a palliative resection and 1 patient in each group was inoperable and underwent colostomy alone. Anaesthesia and medication were identical for both groups with the exception of blood transfusion. Four control and 6 levamisole patients were transfused during surgery. Blood was taken for immunological assessment immediately before surgery and at 3 and 7 days after operation for T cell estimation, and at 1, 14 and 28 days after operation for the tests of lymphocyte function. Further tests were performed at 2 months, if there was persistent immunosuppression.

Immunological assessment

Enumeration of lymphocytes: A total white cell count was performed and lymphocytes were enumerated by a differential white cell count on a Giemsa-stained, air-dried blood film. T cells were enumerated by assessing E rosette formation by the method of Strong et al. (1975). Heparinized blood was centrifuged on a Ficoll–Hypaque gradient and lymphocytes at the interphase were collected, washed in Hanks' solution and counted. Next, 100 µl of lymphocyte suspension with 4×10^6 cells/ml were mixed with 100 µl of heat-inactivated fetal calf serum and 100 µl of 0·5 per cent sheep red cells. The mixture was incubated at 37 °C for 1 h, centrifuged at 200 *g* for 5 min and finally refrigerated at 4 °C for 16 h. The cell button was resuspended by gentle tapping of the tube. The proportion of lymphocytes without rosettes and of lymphocytes with three or more attached sheep red cells was assessed. One hundred rosettes were counted and each experiment was performed in quadruplicate.

Pre- and postoperative results were compared using the Wilcoxon matched pairs signed ranks test and have been expressed as counts ±one standard error.

Antigenic extracts: Extracts rich in large membranous cell fragments were prepared for each patient from normal colonic mucosa taken at least 10 cm from the tumour site and from a portion of the resected tumour using a modification of the method of Jones and Turnbull (1975). The homogenized tumour was centrifuged at 1000 *g* and an aliquot was removed and subjected to further centrifugation at 3000 *g*. The residue was resuspended in half the volume of supernatant. The protein concentration of this suspension was measured using a ultraviolet spectrophotometer and the specimen was stored at −20 °C for use as antigen in the leucocyte migration inhibition test.

Leucocyte migration inhibition test: The method used was that of Søborg and Bendixen (1967). The patient's cells were migrated in plastic wells containing medium alone for controls and medium containing PPD (200 µg/ml) to test tuberculin sensitivity. To test tumour-directed cell mediated immunity the wells were filled with medium containing either normal colonic extract or colonic tumour extract. The tumour extract was used at the maximum concentration which had been shown to be non-inhibitory to the migration of leucocytes from a normal patient. This was 100 µg/ml for each patient. The medium used was Eagles MEM with 10 per cent fetal calf serum. Six wells were used for each test and after incubation at 37 °C for 16 h the migration areas were drawn using a microscope with a camera lucida attachment. The areas were then measured by planimetry.

Significant migration inhibition was assessed by the Mann–Whitney U test of ranking. The results have been expressed as the number of patients in each group who, following surgery, had a leucocyte migration inhibition test significantly depressed below that found preoperatively. Comparison between the rates of return of the treatment groups was also made using the Mann–Whitney U test.

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Table I: PATIENT LYMPHOCYTE COUNTS

Patients	Lymphocytes × 10^3/mm^3 (mean ± s.e. mean) Preop.	Days postop. 3	7
Controls (n = 10)	1·49 ± 0·12	1·18 ± 0·15*	1·35 ± 0·25
Levamisole (n = 10)	1·30 ± 0·13	0·92 ± 0·20	1·20 ± 0·18

* Significant difference from preoperative count, $P<0{\cdot}05$.

Table II: E ROSETTE COUNTS

Patients	E rosettes × 10^3/mm^3 (mean ± s.e. mean) Preop.	Days postop. 3	7
Controls (n = 10)	1·09 ± 0·13	0·81 ± 0·12*	0·97 ± 0·17
Levamisole (n = 10)	0·87 ± 0·09	0·67 ± 0·16	0·86 ± 0·14

* Significant difference from preoperative count, $P<0{\cdot}05$.

Table III: PATIENTS WITH A DEPRESSED LEUCOCYTE MIGRATION INHIBITION TEST FOLLOWING SURGERY (PPD)

Patients	Days 3	7	14	28	>28
Controls (n = 9)	9	7	4	2	0
Levamisole (n = 8)	1	0			

$P<0{\cdot}001$.

Table IV: PATIENTS WITH A DEPRESSED LEUCOCYTE MIGRATION INHIBITION TEST FOLLOWING SURGERY (TUMOUR EXTRACT)

Patients	Days 3	7	14	28	>28
Controls (n = 4)	4	4	4	4	0
Levamisole (n = 3)	2	0			

$P<0{\cdot}05$.

Table V: PATIENTS WITH DEPRESSED LYMPHOCYTE BLASTOGENESIS (PHA-INDUCED) FOLLOWING SURGERY

Patients	No depression following surgery	Days 3	7	14	28	>28
Controls (n = 10)	1	7	6	4	3	0
Levamisole (n = 10)	0	10	9	6	2	0

Lymphocyte blastogenesis: The method used was a modification of that described by Luquetti and Janossy (1976). Heparinized whole blood was diluted 1 in 10 with medium 199. Aliquots of 200 μl of the mixture were placed in separate wells of a multiple culture plate and to each was added either 0·5 μg of purified PHA or an equal volume of phosphate-buffered saline. Culture plates were sealed and incubated for 24 h in 5 per cent CO$_2$ at 37 °C. Following incubation the cultures were labelled with 0·5 μCi of tritiated thymidine and were harvested using a multiple sample harvester following incubation for a further 24 h. The activity of the samples was then determined by liquid scintillation counting.

Results have been expressed as the number of patients who, following surgery, demonstrated a significant depression of thymidine uptake (lymphocyte responsiveness) below that obtained preoperatively. Significance has been assessed by comparing postoperative results with those obtained before surgery using the Wilcoxon matched pairs signed ranks test.

Results

Lymphocyte and E rosette counts

There was a depression of both total lymphocyte and E rosette counts 3 days following surgery in both groups. This reached significance ($P<0{\cdot}05$) in the untreated patients. The counts increased again towards preoperative levels at 7 days. The results are detailed in *Tables I* and *II*.

Leucocyte migration inhibition test

Before surgery 9 control patients and 8 levamisole-treated patients demonstrated leucocyte migration inhibition to PPD. Extract of the patients' own tumour produced migration inhibition in 4 patients in the control group and in 3 patients in the levamisole group. In all patients with positive preoperative tests, these became negative on the first postoperative day. *Tables III* and *IV* express the number of patients in each group with depressed leucocyte migration inhibition on each test day following surgery.

There is a significant difference between the return of migration inhibition of control patients and the levamisole-treated patients for both PPD ($P<0{\cdot}001$) and tumour extract ($P<0{\cdot}05$).

Lymphocyte blastogenesis

There was a depression in the response to PHA, with all but one patient showing a significant fall after operation. The return to preoperative levels was variable in both groups, but when compared with the control patients, levamisole failed to produce a more rapid return to normal. The detailed results are shown in *Table V*.

Discussion

The presence of cell mediated immune depression in cancer patients is associated with a poor prognosis (Eilber et al., 1975). Correction of immune depression by the immunostimulant levamisole has been shown to improve the prognosis of advanced breast cancer (Rojas et al., 1976) and melanoma (Wilkins and Olkowski, 1977).

Riddle and Berenbaum (1967) have shown that surgery causes immunosuppression. This occurs during the period when cancer cells, dissipated by surgical manipulation, may be developing into metastatic foci. The correction of immunosuppression following surgery may help to prevent this problem. In this study an attempt has been made to reduce the degree and duration of immunosuppression following surgery by the use of levamisole. In immunosuppressed patients, levamisole has been found to restore delayed hypersensitivity (Tripodi et al., 1973) and to increase leucocyte migration inhibition to specific antigens (Goebel et al., 1977). T lymphocytes and their response to mitogens have also been shown to be augmented by the use of levamisole *in vivo* (Renoux et al., 1977).

Both lymphocyte and E rosette counts were depressed on the third postoperative day in the untreated group of patients. The levamisole-treated patients also demonstrated depressed cell counts at 3 days. The finding that the results did not reach significance in the levamisole group could be accounted for by the larger error in this patient group. By the seventh postoperative day there was a return to preoperative cell counts in both groups. The difference between the postoperative depression of lymphocyte

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References 1. Willis, A.T. (1977) Scottish Medical Journal, 22, 155. 2. Willis, A.T. et al. (1977) British Medical Journal, 1, 607. 3. Finegold, S.M. Anaerobic Bacteria in Human Disease, Academic Press Inc. New York, 1977. 4. Willis, A.T. et al (1975) Journal of Antimicrobial Chemotherapy, 1, 393, 1975.

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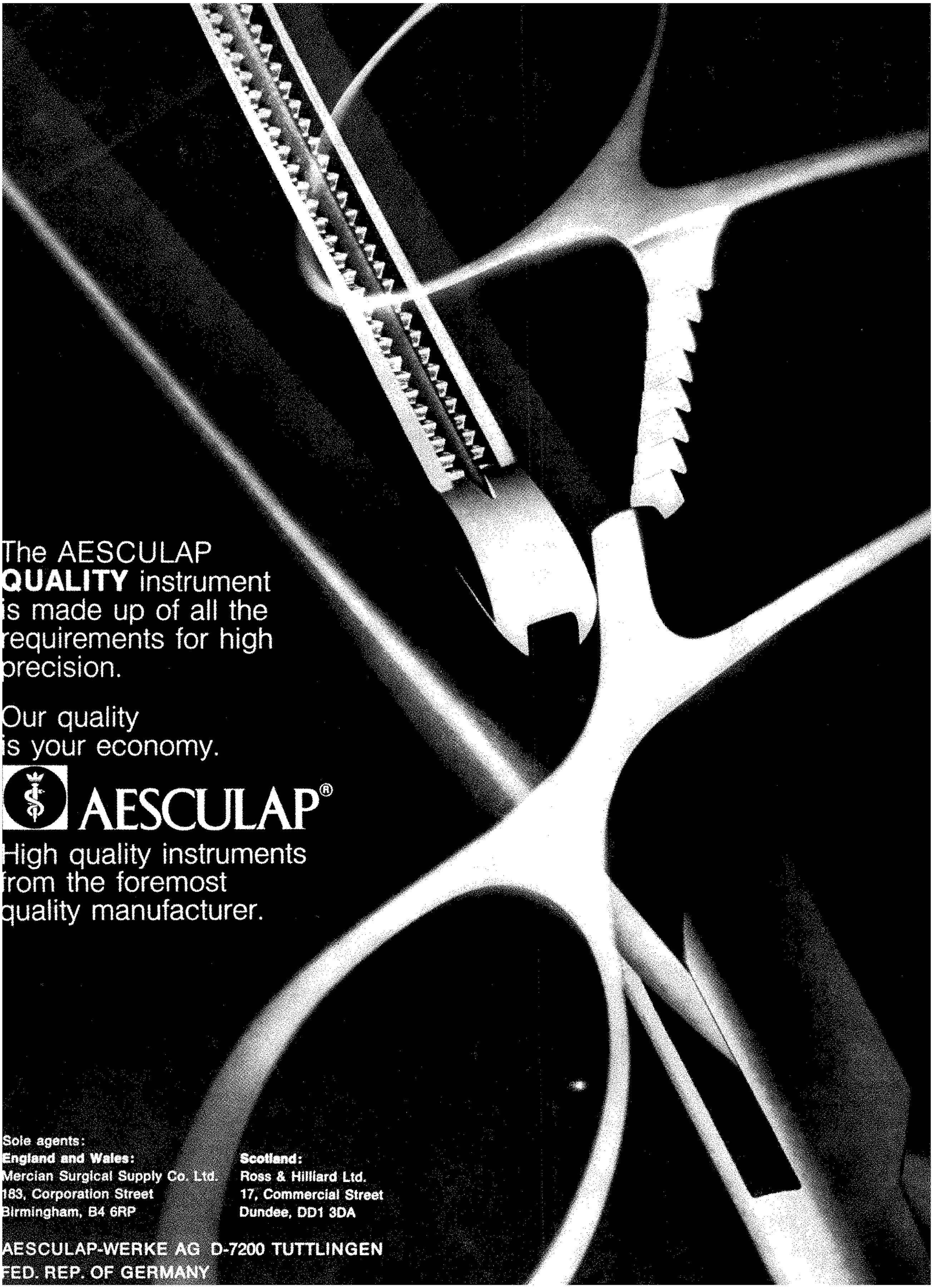

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and E rosette counts in the treated and untreated groups was marginal and further studies need to be made to clarify this.

Leucocyte migration inhibition to tumour extract was demonstrated before surgery by 4 control patients and 3 levamisole patients. Not all patients with colorectal cancer demonstrate migration inhibition to tumour extract (Bull, 1973; Guillou and Giles, 1973). This apparent lack of recognition of tumour antigen has been correlated with extensive disease by Bull (1973), but this was not our experience. Levamisole accelerated the return of preoperative leucocyte migration inhibition following surgery in patients with both local and extensive cancer and abolished the difference between the return of migration inhibition to PPD and that to tumour extract.

The return to preoperative status of PHA-induced blastogenesis was unaffected by levamisole administration. Although at variance with some evidence (Renoux et al., 1977), this observation confirms the studies of Cappel et al. (1975) in the immunosuppressed experimental animal.

The observation that PHA-induced transformation in contrast to leucocyte migration inhibition is unaffected by levamisole is of interest. Leucocyte inhibition measures the production of lymphokines, which are known to be formed in response to a specific antigen. In addition, lymphokines are considered to mediate between stimulated lymphocytes and non-immune macrophages (Fidler, 1975). This has been shown to result in tumour cell destruction *in vitro* (Piessens et al., 1975). As a result, we believe that the leucocyte migration inhibition test is a more specific reflection of the immune status of the cancer patient. In contrast, blastogenesis is a non-specific and perhaps less important expression of the immune response. The ability to produce lymphokines in response to an antigen, against a background of a general depression in cell mediated immunity, is of great interest and may have particular relevance to prognosis following surgery in cancer patients.

References

BULL D. M. (1973) Immunity to colon cancer assessed by antigen-induced inhibition of mixed mononuclear cell migration. *Science* **181**, 957–959.

CAPPEL R., HENRY C. and THIRY L. (1975) Experimental immunosuppression induced by herpes simplex virus. *Arch. Virol.* **49**, 67–72.

COCHRAN A. J., SPILG W. G. S., MACKIE R. M. et al. (1972) Postoperative depression of tumour-directed cell mediated immunity in patients with malignant disease. *Br. Med. J.* **4**, 67–70.

EILBER F. R., NIZZA J. A. and MORTON D. L. (1975) Sequential evaluation of general immune competence in cancer patients: correlation with clinical course. *Cancer* **35**, 660–665.

FIDLER I. J. (1975) Activation *in vitro* of mouse macrophages by syngeneic, allogeneic or xenogeneic lymphocyte supernatants. *J. Natl. Cancer Inst.* **55**, 1159–1163.

GOEBEL K. M., GOEBEL F. D., SCHUBOTZ R. et al. (1977) Levamisole-induced immunostimulation in spondylarthropathies. *Lancet* **2**, 214–217.

GUILLOU P. J. and GILES G. R. (1973) Inhibition of leucocyte migration by tumour associated antigens of the colon and rectum. *Gut* **14**, 733–738.

JONES B. M. and TURNBULL A. R. (1975) Horizontal studies of cell mediated immune reactions to autologous tumour antigens in patients with operable mammary carcinoma. *Br. J. Cancer* **32**, 339–344.

LUQUETTI A. and JANOSSY G. (1976) Lymphocyte activation. VIII. The application of a whole blood test to the quantitative analysis of PHA responsive T cells. *J. Immunol. Methods* **10**, 7–25.

MILLER G. C., PRITCHARD D. J., RITTS R. E. jun. et al. (1976) The effect of surgery on the quantity of lymphocyte subpopulations. *J. Surg. Res.* **21**, 155–158.

PARK S. K., BRODY J. I., WALLACE H. A. et al. (1971) Immunosuppressive effects of surgery. *Lancet* **1**, 53–55.

PIESSENS W. F., CHURCHILL W. H. and DAVID J. R. (1975) Macrophages activated *in vitro* with lymphocyte mediators kill neoplastic but not normal cells. *J. Immunol.* **114**, 293–299.

RENOUX G., RENOUX M. and PALAT A. (1977) Influences on T cell reactivity and on survival of untractable cancer patients. In: CHIRIGOS M. A. (ed.) *Modulation of Host Immune Resistance in the Prevention and Treatment of Induced Neoplasms.* Fogarty International Center Proceedings No. 28; Washington, US Government Printing Office, p. 77.

RIDDLE P. R. and BERENBAUM M. C. (1967) Postoperative depression of the lymphocyte response to phytohaemagglutinin. *Lancet* **1**, 746–748.

ROJAS A. F., MICKIEWICZ E., FEIERSTEIN J. N. et al. (1976) Levamisole in advanced human breast cancer. *Lancet* **1**, 211–215.

SØBORG M. and BENDIXEN G. (1967) Human leucocyte migration as a parameter of hypersensitivity. *Acta Med. Scand.* **181**, 247–255.

STRONG D. M., WOODY J. N., FACTOR M. A. et al. (1975) Immunological responsiveness of frozen-thawed human lymphocytes. *Clin. Exp. Immunol.* **21**, 442–455.

TRIPODI D., PARKS L. C. and BRUGMANS J. (1973) Drug-induced restoration of cutaneous delayed hypersensitivity in anergic patients with cancer. *N. Engl. J. Med.* **289**, 354–357.

VERHAEGEN H., DE CREE J., VERBRUGGEN F. et al (1973) Immune responses in elderly cutinegative subjects and the effect of levamisole. *Verh. Dtsch. Ges. Inn. Med.* **79**, 623–628.

WILKINS S. A. jun. and OLKOWSKI Z. L. (1977) Immunocompetence of cancer patients treated with levamisole. *Cancer* **39**, 487–493.

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Cimetidine in the treatment of peptic ulceration following renal transplantation

G. WILLIAMS AND J. E. CASTRO*

SUMMARY

Seven patients who developed peptic ulceration following renal transplantation have been treated by cimetidine. One died before its value could be assessed. The remaining 6 were symptom-free within 48 h. In 3 patients the ulcer appeared healed on gastroscopy, in one there was no change, another required operation for gastrointestinal bleeding 1 month after beginning cimetidine and the other patient has been lost to follow-up after 5 months' treatment. Two patients had a significant rise of serum creatinine whilst on the drug, but there is no evidence of increased immunological reactivity towards the graft and no agranulocytosis.

THERE is a high incidence of peptic ulceration and related complications in patients on chronic haemodialysis or those who have received renal allografts. Peptic ulcer disease occurred in 48 per cent of patients on regular haemodialysis, and of these 15 per cent bled after transplantation (Doherty et al., 1977). Patients may develop severe dyspepsia or gastrointestinal perforation. Such complications have a high mortality, for of 144 transplants, 14 had upper gastrointestinal bleeding and, despite surgery, all died (Moore and Hume, 1969). Fifteen per cent of our own patients, without dyspepsia during dialysis, developed symptoms within 3 months of transplantation; of these, 6 had gastrointestinal bleeding and 4 of them died (Chisholm et al., 1977).

Cimetidine, a histamine H_2-receptor antagonist, is of increasing interest in the treatment of peptic ulcer (Domschke et al., 1977; Gillespie et al., 1977). Rapid symptomatic relief with healing of the ulcer and avoidance of operation has considerable advantages, especially in uraemic or immunosuppressed patients. However, there is doubt concerning the use of cimetidine in patients with renal transplants. Significant increases in mean plasma creatinine have been reported after administration of the drug (Blackwood et al., 1976; Haggie et al., 1976), and this could be confused with graft rejection, though Jones et al. (1978) showed no alteration in biochemistry in their patients. Furthermore, agranulocytosis after cimetidine has been described (Craven and Whittington, 1977), and combination with azathioprine may result in severe bone-marrow toxicity causing azathioprine to be stopped. In mice, H_2-receptor antagonists inhibit histamine-mediated T lymphocyte cytolysis (Plaut et al., 1973). Cimetidine also prevents histamine-mediated migration inhibition of immune guinea-pig peritoneal exudate cells (Rocklin, 1975). A limited study in humans showed that cimetidine had no effect on mean lymphocyte migration inhibition by BCG and antibody production, but it did cause lower serum concentrations of IgA and IgM in some patients, and increased response to BCG in others (McGregor et al., 1977). No immunological abnormalities were detected during 2 years (De Pauw et al., 1977) of cimetidine treatment of patients with Zollinger–Ellison syndrome.

The high morbidity and mortality associated with peptic ulcer disease in patients after renal transplantation caused us to study the effects of cimetidine in 7 transplanted patients with proved ulcers.

Case reports

Case 1: A 24-year-old male with Still's disease had received prednisone for 11 years. After a haematemesis in 1967 a barium meal showed a duodenal ulcer. X-ray in 1975 was normal, but further radiology after a haematemesis in May 1976 again demonstrated the ulcer. In September 1976 he received a live donor transplant from his father for terminal renal failure due to amyloidosis. Three weeks postoperatively the serum creatinine was 120 μg/l. One month later abdominal pain necessitated gastroscopy which showed hypertrophic rugae and an active chronic duodenal ulcer. There was normal basal acid levels with a raised output after pentagastrin stimulation. Cimetidine 200 mg t.d.s. and 400 mg *nocte* was begun. After 24 h the patient was symptom-free but repeat gastroscopy 5 months later showed no healing. At this time basal and pentagastrin-stimulated acid output were within the normal range. The patient has now received cimetidine at the above dosage for 10 months. There has been no evidence of allograft rejection, serum creatinine has not changed and the white cell count is normal.

Case 2: A male aged 25 years with end-stage renal failure due to hypertension received a live donor allograft from his monther in November 1976. Two rejection episodes were treated with 4 g of methyl prednisolone i.v. One month postoperatively the serum creatinine level was 150 μg/l. Four weeks later the patient had epigastric pain for 3 days and gastroscopy showed two active acute duodenal ulcers. Acid studies were not performed. Cimetidine 200 mg t.d.s. and 400 mg *nocte* was commenced with rapid symptomatic improvement. Gastroscopy after 3 months showed no evidence of duodenal ulcer and the basal acid level was normal, although pentagastrin-stimulated output was slightly elevated. Cimetidine was gradually reduced and stopped over 2 weeks and the patient remained symptom-free. There were no further rejection episodes during cimetidine treatment but serum creatinine rose from 150 to 170 μg 3 weeks after beginning the drug. Values returned to 150 μg/l 1 week after treatment was stopped and the white cell count was unchanged during this period.

Case 3: A 57-year-old male with end-stage renal failure due to hypertension underwent cadaver renal transplant in December 1976. In the first postoperative month he had one rejection episode. Three months later he had upper abdominal pain but gastroscopy was normal. Four weeks later melaena necessitated further gastroscopy, which then showed an active duodenal ulcer. Cimetidine was begun but 4 h later heavy gastrointestinal bleeding necessitated emergency vagotomy and antrectomy. The patient died postoperatively from myocardial infarction.

Case 4: A 30-year-old male with chronic renal failure secondary to chronic glomerulonephritis underwent a cadaver renal transplant in February 1977. Postoperatively he had repeated rejection episodes treated with high doses of steroid. One month later he had upper abdominal pain, but gastroscopy was normal, although barium meal showed a large gastric ulcer. Cimetidine 200 mg t.d.s. and 400 mg *nocte* and carbenoxalone 100 mg t.d.s. was commenced with good symptomatic relief. In April 1977 the patient had massive haematemesis and melaena but at operation there was no gastric ulcer but a large bleeding duodenal ulcer. This was treated by vagotomy and antrectomy with under-running of the ulcer and the postoperative progress was unremarkable. Subsequently, a non-functioning rejected allograft was removed. While on treatment with cimetidine renal function continued to deteriorate slowly with an increase in serum creatinine and a fall in glomerular filtration rate. There was no alteration in the white cell count.

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Case 5: A 37-year-old male underwent a second renal transplant in October 1969. Eight years later epigastric pain for 2 weeks necessitated gastroscopy, which showed a small active duodenal ulcer. Gastric acid studies were not performed. Cimetidine 200 mg t.d.s. and 400 mg *nocte* was commenced with complete symptomatic relief within 48 h. Repeat gastroscopy 2 months later showed a healed duodenal ulcer and cimetidine was slowly reduced and stopped over 4 weeks. Serum creatinine rose from 130 µmol/l to 150 µmol/l during treatment, but fell to 115 µmol/l 1 week after stopping the drug. There was no evidence of allograft rejection and no alteration in the white cell count.

Case 6: A 61-year-old male with chronic renal failure due to chronic glomerulonephritis had a live donor transplant in 1974. After many rejection episodes, serum creatinine stabilized at 300 µmol/l. In 1977 the patient complained of upper abdominal pain and both barium meal and gastroscopy confirmed an active duodenal ulcer. Cimetidine 200 mg t.d.s. and 400 mg *nocte* was commenced and symptomatic improvement was excellent. After 2 months the cimetidine dose was halved. The patient subsequently returned to his own country and no further clinical details are available. During the first 2 months of cimetidine there was no deterioration of renal function or alteration of the white cell count.

Case 7: A 41-year-old female with chronic renal failure due to chronic glomerulonephritis underwent a live donor transplant in 1971. In 1977 she developed upper abdominal pain and gastroscopy showed a duodenal ulcer. Cimetidine 200 mg t.d.s. and 400 mg *nocte* gave good symptomatic relief. Repeat gastroscopy showed healing of the ulcer and cimetidine was stopped. There was no recurrence of symptoms during treatment and there was no alteration in the creatinine level or the white cell count.

All 7 patients were taking prednisolone and azathioprine during cimetidine therapy. Some were taking antihypertensives as necessary.

Discussion

These preliminary studies show cimetidine to be of some value in the management of patients who develop peptic ulceration following renal transplantation. The previously reported immunological effects of H_2-receptor antagonists did not appear to provoke allograft rejection. Of the 7 patients in this series, 3 showed a rise in serum creatinine whilst on treatment. In 1 patient (*Case* 4), this could be explained by chronic allograft rejection, but in the other 2 (*Cases* 2 and 5) this was probably attributable to cimetidine, for serum creatinine fell to pre-treatment levels soon after the drug was stopped. The rise of the creatinine level was slow and only just reached significant levels. There were no other features to suggest graft rejection, and although this has to be considered, we have found no difficulty in distinguishing this rise from that which would occur during a rejection episode. Agranulocytosis has not been seen in any of our patients, despite concomitant therapy with azathioprine.

The healing of peptic ulcers following therapy with cimetidine was encouraging. Apart from 1 patient (*Case* 3) who died within 16 h of beginning treatment, all the patients had rapid symptomatic relief. In 3 patients the ulcers healed. In one the gastroscopic appearances remain the same after 5 months whilst another had surgery for severe intestinal bleeding 1 month after commencing cimetidine. The remaining patient has remained abroad but he was known to be symptom-free 5 months after commencing treatment.

From the results of these preliminary studies it appears to be safe to give cimetidine to patients who develop peptic ulceration after transplantation; rapid healing of the ulcer can be expected in some patients. Further studies are necessary to determine the efficiency of the treatment and whether prophylactic therapy is valuable for lowering the high incidence of ulceration in such patients.

References

BLACKWOOD W. S., MAUDGAL D. P., PICKARD R. G. et al. (1976) Cimetidine in duodenal ulcer—controlled trial. *Lancet* **1**, 174–176.

CHISHOLM G. D., MEE A. D., WILLIAMS G. et al. (1977) Peptic ulceration, gastric secretion and renal transplantation. *Br. Med. J.* **1**, 1630–1633.

CRAVEN E. R. and WHITTINGTON J. M. (1977) Agranulocytosis four months after cimetidine therapy. *Lancet* **2**, 294–295.

DE PAUW B. E., LAMERS C. B. H. E., WAGENER F. J. T. et al. (1977) Immunological studies after long term H_2-receptor antagonist therapy. *Lancet* **2**, 616.

DOHERTY C. C., O'CONNOR F. A., BUCHANAN K. D. et al. (1977) Peptic ulcer in renal failure. *Gut* **18A**, 964.

DOMSCHKE W., DOMSCHKE S. and DEMLING L. (1977) A double-blind study of cimetidine in patients with duodenal ulceration: clinical, kinetic and gastric and pancreatic secretory data. In: BARLAND W. L. and SIMPKINS M. A. (ed.) *Proceedings of the 2nd International Symposium on Histamine H_2-Receptor Antagonists*. Amsterdam, Excerpta Medica, pp. 217–233.

GILLESPIE G., GARY G. R., SMITH I. S. et al. (1977) Short-term and maintenance cimetidine treatment in severe duodenal ulceration. In: BARLAND W. L. and SIMPKINS M. A. (ed.) *Proceedings of the 2nd International Symposium on Histamine H_2-Receptor Antagonists*. Amsterdam, Excerpta Medica, pp. 240–277.

HAGGIE S. J., FERMONT D. C. and WYLLIE J. H. (1976) Treatment of duodenal ulcer with cimetidine. *Lancet* **2**, 983–984.

JONES R. H., RUDGE C. J., BEWICK M. et al. (1978) Cimetidine: prophylaxis against upper gastrointestinal haemorrhage after renal transplantation. *Br. Med. J.* **1**, 398–400.

MCGREGOR C. G. A., COCHRAN A. J., OGG L. J. et al. (1977) Immunological and other laboratory studies of patients receiving short-term cimetidine therapy. *Lancet* **1**, 122–123.

MOORE T. C. and HUME D. M. (1969) The period and nature of hazard in clinical renal transplantation I. The hazard to patient survival. *Ann. Surg.* **170**, 1–11.

PLAUT M., LICHENSTEIN L. M., GILLESPIE E. et al. (1973) Studies on the mechanisms of lymphocyte mediated cytolysis. III. The role of microfilaments and microtubules. *J. Immunol.* **111**, 89–94.

ROCKLIN R. E. (1975) Regulation of migration inhibitory factor (MIF) production by histamine receptor-bearing lymphocytes. *Fed. Proc.* **34**, 977 (Abstr. 4296).

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Does rectal examination affect serum acid phosphatase levels?

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SUMMARY

Formol-stable serum acid phosphatase (SAP) was measured in 200 patients with symptoms of prostatism, before and at varying time intervals after digital rectal examination. In three separate groups of 50 patients SAP levels were measured before and at 5, 15 and 30 min following rectal examination and in a fourth group of 50 patients it was measured before and at 6, 24 and 48 h after examination. No significant change occurred in SAP levels following this examination in any of the groups studied. We conclude that rectal examination does not raise the SAP and that, contrary to popular belief, blood levels recorded at any time within this 48-h period are reliable.

It has been generally accepted that serum acid phosphatase (SAP) levels measured within 48 h following digital rectal examination may be raised and that the test is therefore unreliable during this period (Woodward, 1959; Longley, 1965; Rains and Ritchie, 1969; Bodansky, 1972; Wilkinson, 1976). The purpose of the present study was to investigate whether the SAP levels altered at different time intervals following this examination. The modified King–Armstrong method used has been well established as a reliable method for measuring prostatic acid phosphatase.

Patients and methods

A total of 200 male patients over the age of 50 years with varying surgical and medical conditions and all with the symptoms of prostatism was subjected to digital rectal examination in the left lateral position by three different surgeons. To standardize the rectal examination as far as possible the following method, as described in *Demonstrations of Physical Signs in Clinical Surgery* by Hamilton Bailey (Clain, 1967), was used and the findings were carefully recorded:

1. Anteriorly—prostate, seminal vesicle, rectovesical pouch. Prostate—size (lobe), consistency, mobility, mucosa, sulcus, induration etc.
2. Left and right lateral rectal wall.
3. Posteriorly—hollow of sacrum and coccyx.

Blood samples were taken before and at intervals of 5, 15 and 30 min following rectal examination in each of the three groups of 50 patients and in a fourth group of 50 patients at intervals of 6, 24 and 48 h.

The SAP levels were determined by a modified King–Armstrong method which is based upon the hydrolysis of p-nitrophenyl phosphate with the liberation of phenol, the phenol so formed being estimated colorimetrically (Dhmori 1937; King and Delory, 1939; Jacobson, 1960). The result, in King–Armstrong units, is expressed as milligrammes of phenol liberated per 100 ml of serum in 15 min at 37 °C, each unit corresponding to the liberation of 1 ml of phenol per 100 ml of serum. Acid phosphatase is very unstable and so the serum was separated immediately and stored at −20 °C. The tests were carried out in small batches.

Erythrocytes contain appreciable acid phosphatase activity and, even in the absence of haemolysis, red cell enzyme may be released into the serum. The addition to the reaction mixture of 0·5 per cent formaldehyde completely inactivates red cell acid phosphatase without inhibiting the prostatic fraction (Abdul Fadl and King, 1948, 1949). The determination is based upon the principle that, in the absence of alkaline oxidizing agents, 4-amino antipyrine gives a red colour with phenolic compounds (Kind and King, 1954, Powell and Smith, 1954).

Table I: SAP LEVELS BEFORE AND AFTER DIGITAL RECTAL EXAMINATION

		Mean	s.d.	t	P value
At 5 min 47 patients (3 excluded; Ca. prostate)	Pre-RE Post-RE	1·75 1·80	±1·64 ±1·63	−0·176	>0·6
At 15 min 49 patients (1 excluded, Ca. prostate)	Pre-RE Post-RE	1·46 1·35	±0·91 ±0·68	0 670	>0·5
At 30 min 48 patients (2 excluded, Ca. prostate)	Pre-RE Post-RE	1·50 1·45	±0·79 ±0·86	0·306	>0·7

Ca., Carcinoma; RE, rectal examination.

Table II: SAP LEVELS BEFORE AND AFTER DIGITAL RECTAL EXAMINATION

		Mean	s.d.	t	P value
At 6 h	Pre-RE Post-RE	1·426 1·359	0·691 0·457	0·556	<0·6>0·5
At 24 h	Pre-RE Post-RE	1·426 1·553	0·691 0·660	0·933	>0·4
At 48 h	Pre-RE Post-RE	1·426 1·304	0 691 0·560	1·0204	>0·3

RE, Rectal examination.

The serum was incubated with citrate buffer, pH 4·9, and p-nitrophenyl phosphate as substrate for 1 h at 37 °C. The reaction was stopped by the addition of 0·5 M sodium hydroxide, 0·5 M sodium bicarbonate, 0·6 per cent 4-amino antipyrine and 2·4 per cent potassium ferricyanide and the extinction measured at 510 nm. The standard was prepared from pure crystalline phenol in HCl. The reference range is 0·5–3·5 KA units/dl (mean ±2 s.d.).

Results

The SAP levels before and following the rectal examination in three different groups of 47, 49 and 48 patients at respective time intervals of 5, 15 and 30 min were analysed by the unpaired Student's t test. In none of these groups was there any significant change in SAP levels following rectal examination (P value >0·6, >0·5, >0·7, *Table I*). In the fourth group of 50 patients the SAP levels at 6, 24 and 48 h were also analysed by the unpaired t test and no significant change between pre- and post-rectal examination SAP levels was demonstrated (P values >0·5, >0·4, >0·3, *Table II*).

It was thought that age might influence SAP levels following rectal examination and therefore the patients were divided into three age groups: 50–59 years (45 patients), 60–69 years (78 patients) and 70 years and over (71 patients). In none of these groups was there any significant change in pre- and post-rectal examination SAP level when analysed by the unpaired t test (P values >0·3, >0·4, >0·9, *Table III*).

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Table III: SAP LEVELS RELATED TO AGE GROUPS

		Mean	s.d.	*t*	*P* value
50–59 yr	Pre-RE	1·31	±0·53	0·915	>0·3
45 patients (1 excluded, Ca. prostate)	Post-RE	1·44	±0·74		
60–69 yr	Pre-RE	1·51	±1·48	1·004	>0·4
78 patients (2 excluded, Ca. prostate)	Post-RE	1·55	±1·50		
70+ yr	Pre-RE	1·60	±1·55	−0·118	>0·9
71 patients (3 excluded, Ca. prostate)	Post-RE	1·57	±1·55		

Ca., Carcinoma; RE, rectal examination.

Table IV: SAP LEVELS IN SIMPLE BENIGN HYPERTROPHY AND COMPLICATED BENIGN HYPERTROPHY

		Mean	s.d.	*t*	*P* value
Benign	Pre-RE	1·41	±0·80	−0·335	0·7
hypertrophy ($n = 149$)	Post-RE	1·37	±0·69		
Complicated	Pre-RE	1·88	±1·87	0·596	0·6
hypertrophy ($n = 45$)	Post-RE	2·13	±1·84		

RE, Rectal examination.

Table V: SAP LEVELS IN 6 PATIENTS WITH CARCINOMA OF THE PROSTATE

Patient	Pre-RE	Post-RE	SAP
1	12·5	11·8	↓
2	5·79	2·37	↓
3	3·0	2·50	↓
4	2·0	4·25	↑ (+2 s.d.)
5	1·5	3·0	↑ (+2 s.d.)
6	2·0	2·0	=

It has been suggested that local complications such as urinary tract infections, recent catheterization or obvious bladder pathology may influence SAP levels. To exclude this possibility the patients were divided in two groups, those with simple hypertrophy alone (149 patients) and those with the above-mentioned complications (45 patients). In neither of these groups was there any significant change in the SAP levels (*P* value >0·7, >0·6, *Table IV*).

In this series 11 out of 194 patients (5·6 per cent) had SAP values below the lower limit of normal before rectal examination. In 3 of these patients the SAP was raised following rectal examination to within normal limits (0·25 to 0·5, 0·25 to 1·0, 0·45 to 0·5). In 1 patient the SAP level fell to below the lower limit of normal (0·75 to 0·25) following examination. In 7 patients it remained unchanged. In this series no patient was found to have a level of 3·5 either before or after examination. Six patients were subsequently found to have histologically proved carcinoma of the prostate and therefore were not included in the following analysis. It is interesting to note that in 6 patients with carcinoma of the prostate there were wider variations in the levels of SAP before and after rectal examination (*Table V*).

Discussion

It has been established that prostatic massage does increase the level of SAP (Woodward, 1959; Wilkinson, 1976), but it appears that a certain amount of confusion has arisen in the past concerning SAP levels following rectal examination or recent catheterization. It has been stated that mild trauma to the prostate, e.g. catheterization or rectal examination, will cause transitory elevation of SAP (Wilkinson, 1976). The instability of SAP may have contributed to previous confusion, not only because it is very labile on storage, but also one previous trial used heparinized blood, and it has been shown that heparin interferes with the analysis of the prostate fraction (Dybkaer and Jenson 1958; Woodward, 1959). Our findings clear the confusion. This is important in outpatient departments where a rectal examination has been done and there is clinical suspicion of prostatic pathology; the SAP level still can be measured reliably on the same sample of blood taken for other biochemical investigations. The patient does not have to wait for 48 h before a second blood sample is taken. It saves time for both surgeon and patient. When a patient presents with acute retention of urine he can safely be catheterized before blood is taken and the SAP level can be relied upon. Raised SAP levels should not be ignored because blood was taken for the estimation within 48 h of a rectal examination.

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References

ABUL-FADL M. A. M. and KING E. J. (1948) Inhibition of acid phosphatases by formaldehyde and its clinical application for determination of serum acid phosphatases. *J. Clin. Pathol.* **1**, 80–90.

ABUL-FADL M. A. M. and KING E. J. (1949) Properties of the acid phosphatases of erythrocytes and of the human prostate gland. *Biochem. J.* **45**, 51–60.

BODANSKY O. (1972) Acid phosphatase. In: SOBOTKA H. and STEWART C. P. (ed.) *Advances in Clinical Chemistry*, vol. 15. New York, Academic Press, p. 43.

CLAIN A. (ed.) (1967) *Hamilton Bailey's Demonstrations of Physical Signs in Clinical Surgery*, 14th ed. Bristol, Wright, p. 245.

DHMORI Y. (1937) Über die Phosphomonoesterase. *Enzymologia* **4**, 217–231.

DYBKAER R. and JENSON G. (1958) Acid phosphatase following prostate massage. *Scand. J. Clin. Lab. Invest.* **10**, 349.

JACOBSSON K. (1960) The determination of tartrate-inhibited phosphatase in serum. *Scand. J. Clin. Lab. Invest.* **12**, 367–380.

KIND P. R. N. and KING E. J. (1954) Estimation of plasma phosphatase by determination of hydrolysed phenol with amino-antipyrine. *J. Clin. Pathol.* **7**, 322–326.

KING E. J. and DELORY G. E. (1939) The rates of enzymic hydrolysis of phosphoric esters. *Biochem. J.* **33**, 1185–1190.

LONGLEY J. R. (1965) The deceptive acid phosphatases. *Calif. Med.* **103**, 343–344.

POWELL M. E. A. and SMITH M. J. H. (1954) Determination of serum acid and alkaline phosphate activity with 4-amino antipyrine. *J. Clin. Pathol.* **7**, 245–248.

RAINS A. J. H. and RITCHIE H. D. (ed.) (1969) *Bailey and Love's Short Practice of Surgery*. London, Lewis, p. 1161.

WILKINSON H. J. (1976) *The Principles and Practice of Diagnostic Enzymology*. London, Arnold, p. 141.

WOODWARD H. W. (1959) The clinical significance of serum acid phosphatase. *Am. J. Med.* **27**, 902–910.

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Sparks mandril, velour Dacron and autogenous saphenous vein grafts in femoropopliteal bypass

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SUMMARY

Ninety-nine consecutive vascular reconstructions with femoropopliteal bypass performed during 1973–6 have been reviewed. A Sparks mandril was used in 11 patients, reversed autogenous saphenous vein in 30 and velour Dacron prostheses in 58. The indication for operation was severe ischaemia in 79 per cent. The overall patency rate at 12 months was 70 per cent for autogenous vein, 46 per cent for velour Dacron prosthesis and 18 per cent for Sparks mandril. When the distal anastomosis was located above the knee the patency rate was 100 per cent and 87 per cent for autogenous vein and velour Dacron graft respectively, while the corresponding figures for distal anastomosis below the knee were 58 per cent and 11 per cent. At follow-up 60 per cent of the patients showed improvement owing to the vascular reconstruction.

MANY methods of revascularization of the lower limb in ischaemia have been recommended. In those techniques in which no 'foreign' material is used, such as thrombendarterectomy (Wylie et al., 1964) or thrombendarterectomy with patch graft, a 5-year patency rate of 42–60 per cent is described (Vollmar et al., 1968). Results at almost the same level are obtained when profundaplasty is used as an alternative method of limb salvage (Martin and Bouhoutsos, 1977). The same results are claimed after extended profundaplasty where a limb salvage rate of approximately 50 per cent has been reported (Martin et al., 1972; Berguer et al., 1973; Cotton and Roberts, 1975). It is quite clear, however, that the majority of authors regard the femoropopliteal bypass procedure as the method of choice for the treatment of obliterative disease of the leg.

Femoropopliteal bypass using autogenous venous transplants was first descibed by Kunlin in 1949. Since then a great many reports have described excellent results with this technique (Szilagyi et al., 1964; Crawford et al., 1966; Darling et al., 1967; DeWeese and Rob, 1977), some of these reports showing a 2-year patency rate of 70–90 per cent and a 10-year patency rate of 40–60 per cent.

As recently as 1975, it was stated by Crawford that: 'As far as the graft is concerned, there is nothing better than a good autogenous saphenous vein graft. Conversely, there is nothing worse than an inadequate autogenous saphenous vein.' A good venous substitute is not always available. The smallest part of the vein to be used should have a minimum of 5 mm external diameter when distended. It should not be diseased and must not be damaged during removal (Barker et al., 1976). Frequently therefore, another arterial substitute has to be found.

In the search for substitutes, synthetic material such as Teflon and Dacron has been tried widely. Dacron grafts in femoropopliteal vascular reconstructions have led to excellent results in the early postoperative phase with a patency rate at the level of 30–60 per cent after 1–5 years (Vollmar et al., 1968; DeBakey et al., 1973). Slightly better results have been recorded when knitted velour Dacron prostheses have been used, with a patency rate of 70 per cent after 5 years often described (DeBakey et al., 1973). A completely different technique involves the use of collagen tubes —Sparks mandril (Sparks, 1973). However, up to now the results have not been acceptable, with a patency rate after 2 years of 26 per cent (Hallin and Sweetman, 1976).

This present study compares the results of femoropopliteal reconstructive surgery utilizing Sparks mandril, velour Dacron and autogenous saphenous vein grafts. Special emphasis is placed on factors relating to graft failure and other complications of importance in limb salvage.

Patients and methods

Patients

From January 1973 to December 1976 99 consecutive femoropopliteal bypass reconstructions were carried out in 21 women and 78 men with arteriosclerotic obliterative disease of the lower limb. The average age was 62 years (range 25–87 years). The autogenous saphenous vein was used if the vein was available and after excision could be distended to at least 5 mm in diameter. When a suitable vein was not available a velour Dacron graft or Sparks mandril was used. The number of patients in each group is shown in *Table I*. Seventy-three patients had a severe ischaemia of the lower extremity (including rest pain, with or without gangrene), while 26 patients had a disabling intermittent claudication. The average duration of symptoms before operation was 25 months (range 1–122 months). The follow-up was from 1 year up to 5 years.

Table I: TYPE OF ARTERIAL SUBSTITUTE IN PATIENTS WITH SYMPTOMS OF SEVERE ISCHAEMIA AND INTERMITTENT CLAUDICATION

Arterial substitute	No. patients with severe ischaemia	No. patients with claudication	Total
Velour Dacron	46	12	58
Autogenous saphenous vein	20	10	30
Sparks mandril	7	4	11
Total	73	26	99

Run-off classification

The run-off was classified according to the run-off index described by Morton et al. (1967). Points are awarded to the distal popliteal artery and each of its branches, as seen on angiograms in two different projections. Each patent artery scores 4 points, 25 per cent stenosis 3 points, 50 per cent stenosis 2 points, 75 per cent stenosis 1 point and a total occlusion of the artery, zero. A normal angiogram of the calf vessels, therefore, yields 16 points. The patients were divided into three groups according to this index: stage I, patients with 16–12 points; stage II, patients with 11–7 points; and stage III, patients with 6–0 points.

Clinical physiology

Distal pressure measurement of the big toe was performed in all the patients using the strain-gauge technique (Gundersen, 1972) preoperatively and approximately 1 month postoperatively.

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Velour Dacron graft

Fifty-eight patients were treated with a DeBakey Vasculour-D knitted velour Dacron arterial graft 6 mm in diameter. Twenty-two patients had had previous vascular reconstructions in the lower leg. Twenty-eight patients had gangrene of the foot or toes Seventy-one per cent of the patients were heavy smokers. At operation an end-to-side anastomosis was performed to the common femoral artery above the bifurcation and distally an end-to-side anastomosis to the popliteal artery, in 39 cases above the knee and in 19 cases below the knee. All grafts were pre-clotted.

Sparks mandril

Sparks mandrils were used in 11 cases. The silicone mandril consists of a smooth silicone rubber rod (outside diameter 6 mm) covered with two layers of large mesh, knitted Dacron tubes. It is implanted subcutaneously in the thigh, through the popliteal fossa to the calf (Sparks, 1973). After at least 6 weeks, during which time an autogenous tube grows around the mandril, encapsulating the Dacron tube, the silicone rod is withdrawn and the new Dacron-reinforced autogenous graft is anastomosed end-to-side to the common femoral artery and the distal popliteal artery below the knee in all cases. Three patients had had previous vascular reconstructions. Three patients had gangrene of the toe or foot: 73 per cent were heavy smokers.

Autogenous saphenous vein grafts

Thirty patients had a reversed autogenous saphenous vein graft with the distal anastomosis below the knee in 12 cases and above the knee in 18. The proximal anastomosis was in all cases made in the common femoral artery. Four patients had had earlier vascular reconstructions. Eight patients had gangrene in the foot or toe: 67 per cent of the patients were heavy smokers.

Results

Postoperative complications

Early graft thrombosis within 1 month was seen in 29 per cent of the cases while late thrombosis occurred in 25 per cent of the series. Postoperative wound infections were seen in 17 per cent. However, most of these infections were noted during 1973–4. Since we instituted better hygienic routines and prophylactic antibiotics in 1975 there has been very little infection (Christenson et al., 1979). Postoperative pulmonary insufficiency was recorded in 5 patients, as was myocardial infarction. Postoperative haemorrhage was noticed in 4 patients of whom 3 were re-explored. As regards the differences between the three types of graft, there was early graft thrombosis in 7 of the Sparks mandril cases, in 18 of 58, velour Dacron grafts and in 4 of 30 autogenous vein reconstructions. Successful thrombectomy with good long term results was performed in 13 of the 18 patients with a velour Dacron prosthesis. The same was true for 1 of the 4 patients in the autogenous vein group and for the only patient requiring thrombectomy in the Sparks mandril group (*Table II*). Thrombectomy in late graft thrombosis (12 velour Dacron grafts) was unsuccessful in all cases.

Mortality

The hospital mortality within 1 month of operation was 4 per cent (3 patients in the velour Dacron group and 1 patient in the autogenous saphenous vein group). The cause of death was myocardial infarction. There was no mortality in the group where the indication for operation was intermittent claudication. The late mortality was 6 per cent; in 1 case this was due to a pancreatic cancer, but in the remaining patients it was because of myocardial infarction.

Table II: COMPLICATIONS WITH EARLY AND LATE GRAFT THROMBOSIS IN RELATION TO TYPE OF ARTERIAL SUBSTITUTE

	Early graft thrombosis		Late graft thrombosis		Total	
Arterial substitute	No.	%	No.	%	No.	%
Velour Dacron	18	31	14	24	32	55
Autogenous saphenous vein	4	13	9	30	13	43
Sparks mandril	7	64	2	18	9	82

Table III: FREQUENCY OF AMPUTATION RELATED TO RUN-OFF INDEX AND TYPE OF GRAFT

	Run-off index		
	Stages I+II	Stage III	Total
Sparks mandril			
No.	9	2	11
Amputation	0 (0)	2 (100)	2 (18)
Velour Dacron			
No.	39	19	58
Amputation	12 (31)	10 (53)	22 (38)
Autogenous saphenous vein			
No.	23	7	30
Amputation	3 (13)	2 (29)	5 (16)
Total			
No.	71	28	99
Amputation	16 (23)	13 (46)	29 (29)

Figures in brackets are percentages.

Table IV: FREQUENCY OF AMPUTATION RELATED TO TYPE OF GRAFT, LOCATION OF THE DISTAL ANASTOMOSIS AND RUN-OFF INDEX

	Arterial substitute			
	Velour Dacron		Autogenous saphenous vein	
Run-off index and amputation rate	A-k ($n = 34$)	B-k ($n = 19$)	A-k ($n = 18$)	B-k ($n = 12$)
Stage I				
No.	11	6	8	5
Amp.	0	5	0	2
Stage II				
No.	15	7	7	3
Amp.	1	6	0	1
Stage III				
No.	13	6	3	4
Amp.	4	6	0	2

A-k, above-knee; B-k, below-knee.

Follow-up study

All patients have been followed up for at least 12 months. The patency rate after 12 months was 70 per cent for autogenous saphenous vein graft, 46 per cent for velour Dacron prosthesis and 18 per cent for Sparks mandril. Several of the grafts are functioning after a longer time. One Sparks mandril has been patent for 38 months. This graft was implanted subcutaneously for 6 months before it was used for reconstruction.

The early patency rate in relation to the location of distal anastomosis was good when this anastomosis was above the knee, with 100 per cent patency for the autogenous vein graft and 87 per cent patency for the velour Dacron graft. There were no significant differences between the two types of graft. When the distal anastomosis was below the knee the autogenous

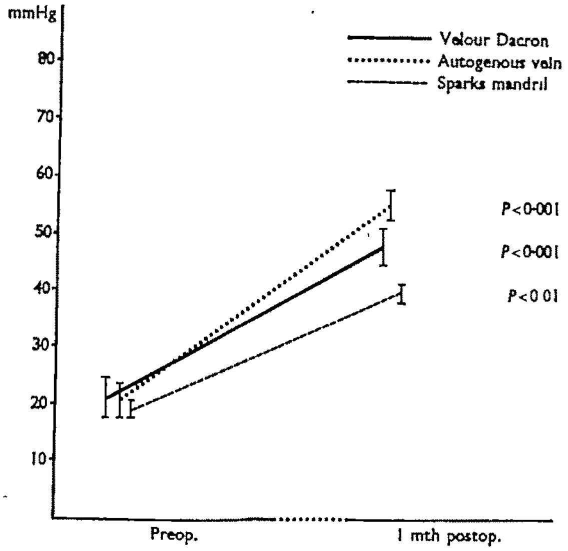

Fig. 1. Pre- and postoperative distal blood pressure in the big toe of the reconstructed leg (mean ± s.e. mean).

vein graft had a patency rate of 58 per cent, which was significantly higher ($P < 0{\cdot}01$) than that of 11 per cent for velour Dacron grafts.

Further reconstructions were performed after failure of the primary operation. In the autogenous vein graft group 1 patient had an axillofemoral bypass and 1 patient had a new femoropopliteal bypass. In the velour Dacron group 2 patients had iliofemoral bypass, 1 patient an axillofemoral bypass and 2 patients another femoropopliteal bypass. Two patients in the Sparks mandril group were further reconstructed with a femoropopliteal bypass.

The amputation rate was 38 per cent in patients with severe ischaemia and one patient with intermittent claudication had an amputation. This patient had a bad run-off (stage II) combined with advanced diabetes mellitus and the indication for operation was dubious. If the run-off was classified as stage I or II there were no differences in the amputation rate, showing 21 per cent and 24 per cent respectively, while it was doubled (46 per cent) in cases with stage III run-off ($P < 0{\cdot}02$). A bad run-off index (stage III) in the velour Dacron group resulted in the highest amputation rate—53 per cent (*Table III*).

The effect of the location of the distal anastomosis on the amputation rate is shown in *Table IV*. Five of 12 patients with the autogenous vein graft below the knee had amputations and 17 of 19 patients in the group with the velour Dacron prosthesis below the knee. When the distal anastomosis was above the knee in patients with autogenous vein grafts there were no amputations, while there were 5 amputations in 39 patients with velour Dacron grafts, all in stage II and III patients.

Distal blood pressure in the big toe was investigated in all patients before operation and again in patients who had not had amputations about 1 month after reconstruction (*Fig.* 1). A statistically significant increase in pressure was noted.

At follow-up the patients were classified as improved if their symptoms had disappeared, tissue lesions had healed and they had been able to resume their normal activity. Sixty patients had improved while 39 were unchanged or worse, resulting in amputation in 29 of these patients. All amputations were below the knee and in at least 13 patients the vascular reconstruction contributed to lowering the level of amputation. Of the amputees, 76 per cent tolerated their leg prosthesis and were well rehabilitated.

Discussion

Patients with distal arteriosclerotic disease with symptoms of severe ischaemia can be managed in several ways, e.g. with femoropopliteal bypass procedures in order to improve their symptoms, save the limb or at least lower the level of a demanded amputation. The use of autogenous vein grafts is well documented as either a reversed or an *in situ* bypass (Skagseth and Hall, 1973). We have also had good results using the reversed great saphenous vein, with a patency rate of 70 per cent after 12 months. If the distal anastomosis is placed above the knee, patency is 100 per cent, while reconstructions below the knee reduce the patency rate to 58 per cent.

When a suitable autogenous vein is not available, different synthetic materials have been used. It has been reported (Crawford, 1975) that 8-mm knitted Dacron grafts with the distal anastomosis below the knee give the same patency rate as that achieved with the reversed autogenous vein. Our findings do not corroborate these results. Velour Dacron grafts with the distal anastomosis above the knee gave a patency rate after 12 months of 87 per cent, which is good, while the patency rate was reduced to an unacceptable 11 per cent if the distal anastomosis was below the knee. The distal run-off was worse in patients receiving velour Dacron grafts, with 70 per cent of patients classified as stage II–III compared with 58 per cent of patients with autogenous vein grafts.

The enthusiastic report on the use of Sparks mandril (Sparks, 1973) has not been verified in our study. We achieved a patency rate after 12 months of only 18 per cent. It is interesting to note, however, that one Sparks mandril has been patent for more than 3 years. This mandril was introduced subcutaneously for 6 months before it was used for reconstruction.

The search for new and better synthetic vascular grafts for below-knee reconstructions in the absence of an adequate autogenous vein is important. The Gore-Tex graft (expanded polytetrafluoroethylene) has in several preliminary reports shown a good patency in below-knee reconstructions: 89 per cent patency after 3 months (Veith et al., 1977), cumulative patency rate within 18 months of 59 per cent (Haimov et al., 1977), and 85 per cent within 20 months (Raithel and Groitl, 1977).

The umbilical cord vein chemically treated in different ways (with alcohol, formalin or glutaraldehyde) has been reported to have good properties for use below the knee and a cumulative patency rate of 70 per cent after 16 months has been reported (Dardik et al., 1976). However, it is equally important to develop preoperative methods to evaluate the run-off of the distal leg and foot in order to choose the right patients for this limb salvage operation.

Bibliography

BARKER W. F., CRAWFORD E. S., MANNICK J. A. et al. (1976) The current status of femoropopliteal bypass for arteriosclerotic occlusive disease: a panel discussion. *Surgery* **79**, 30.

BERGUER R., COTTON L. T. and SABRI S. (1973) Extended deep femoral angioplasty. *Br. J. Med.* 1, 469–471.

CHRISTENSON J. T., EKLOF B., HEDSTROM S.-Å. et al. (1979) Dicloxacillin in prevention of synthetic arterial graft infections. (Submitted for publication.)

COTTON L. T. and ROBERTS V. C. (1975) Extended deep femoral angioplasty: an alternative to femoropopliteal bypass. *Br. J. Surg.* 62, 340–343.

CRAWFORD E. S. (1975) Paper presented at a symposium on femoropopliteal arterial reconstructions. Boston, Mass., Society of Vascular Surgeons.

CRAWFORD E. S., GARRETT H. E., DEBAKEY M. E. et al. (1966) Occlusive disease of the femoral artery and its branches. *Surg. Clin. North Am.* 46, 991–996.

DARDIK H., IBRAHIM J. M., SPRAYREGEN S. et al. (1976) Clinical experience with modified human umbilical cord vein for arterial bypass. *Surgery* 79, 618–624.

DARLING R. C., LINTON R. R. and RAZZUK M. A. (1967) Saphenous vein bypass grafts for femoropopliteal occlusive disease: a reappraisal. *Surgery* 61, 31–40.

DEBAKEY M. E., NOON G. P., DANIELL M. B. et al. (1973) Dacron velour vascular prosthesis: analysis of 425 femoral popliteal bypass grafts. Paper presented at the meeting of the International Cardiovascular Society in Barcelona, Spain, September 1973.

DEWEESE J. A. and ROB C. G. (1977) Autogenous venous grafts ten years later. *Surgery* 82, 775.

GUNDERSEN J. (1972) Segmental measurements of systolic blood pressure in the extremities including the thumb and the great toe. *Acta Chir. Scand.* Suppl. 426.

HAIMOV M., GIRON F. and JACOBSON J. J. (1977) Expanded polytetrafluoroethylene grafts as a vascular substitute in man. Paper presented at the XIII World Congress of the International Cardiovascular Society, Tokyo, Japan, September 1977.

HALLIN R. W. and SWEETMAN W. R. (1976) The Sparks mandril graft. A seven-year follow-up of mandril grafts placed by Charles H. Sparks and his associates. *Am. J. Surg.* 132, 221–222.

KUNLIN J. (1949) Le traitément de l'artérite oblitérante par la greffe veineuse. *Arch. Mal. Cœur* 42, 371–372.

MARTIN P. and BOUHOUTSOS J. (1977) The medium term results after profundoplasty. *Br. J. Surg.* 64, 194–196.

MARTIN P., FRAWLEY J. E., BARBAS A. P. et al. (1972) On the surgery of atherosclerosis of the profunda femoris artery. *Surgery* 71, 182–185.

MORTON D. L., EHRENFELD W. K. and WYLIE E. J. (1967) Significance of outflow obstruction after femoropopliteal endarterectomy. *Arch. Surg.* 94, 592–599.

RAITHEL D. and GROITL H. (1977) Early results with a new vascular prosthesis for arterial reconstruction. Paper presented at the XIII World Congress of the International Cardiovascular Society, Tokyo, Japan, September 1977.

SKAGSETH E. and HALL K. V. (1973) *In situ* vein bypass. Experience with new vein valve strippers. *Scand. J. Thorac. Cardiovasc. Surg.* 7, 53–56.

SPARKS C. H. (1973) Silicone mandril method for growing reinforced autogenous femoro-popliteal artery grafts *in situ*. *Ann. Surg.* 177, 293–297.

SZILAGYI D. E. (1964) Ten years' experience with aortoiliac and femoropopliteal arterial reconstruction. *J. Cardiovasc. Surg.* 5, 502–508.

SZILAGYI D. E., SMITH R. F. and ELLIOT J. P. (1964) Venous autografts in femoropopliteal arterioplasty. *Arch. Surg.* 89, 113–125.

VEITH E. J., MOSS C. M. and HAIMOVICI H. (1977) Comparison of polytetrafluoroethylene (PTFE) and autologous saphenous vein grafts in high-risk arterial reconstruction for limb salvage. Paper presented at the XIII World Congress of the International Cardiovascular Society, Tokyo, Japan, September 1977.

VOLLMAR J. (1975) *Rekonstruktive Chirurgie der Arterien.* Stuttgart, Thieme, pp. 286–290.

VOLLMAR J., TREDE M., LAUBACH K. et al. (1968) Principles of reconstructive procedures for chronic femoropopliteal occlusions. Report on 546 operations. *Ann. Surg.* 2, 215–223.

WYLIE E. J., BINKLEY F. M. and ALBO R. J. (1964) Femoropopliteal endarterectomy; operative modifications and consideration of effects of outflow lesions. *Am. J. Surg.* 108, 215–223.

Paper accepted 11 October 1978.

Br. J. Surg. Vol. 66 (1979) 518–521

Reduction in road fatalities and injuries after legislation for compulsory wearing of seat belts: experience in Victoria and the rest of Australia

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SUMMARY

In 1970 the Government of the State of Victoria became the first in the 'western' world to introduce legislation for compulsory wearing of seat belts. Within 14 months the other Australian states followed. Seat belt wearing rates increased to attain 90 per cent in 1977.

This paper presents an evaluation of changes during the period 1955–77 in the incidence of road crash fatalities and injuries for vehicle occupants in Victoria and the rest of Australia.

The introduction of the legislation in Victoria and subsequently in the other Australian states coincided with significant and marked decreases in driver and passenger fatality and injury rates (numbers per 10 000 registered vehicles). The decreases were enough to reduce the total numbers of vehicle occupant fatalities and injuries for all post-legislation years in Victoria. The improvements have been maintained throughout the entire post-legislation period.

The legislation did not apply to child passengers of less than 8 years of age and the frequency of seat belt or harness wearing among them remained low. These children did not share in the overall improvement for passengers.

The Australian experience supports the view that legislation for compulsory wearing of seat belts is the single most effective method available for the protection of vehicle occupants in road crashes.

A CAMPAIGN for compulsory wearing of seat belts initiated by the Road Trauma Committee of the Royal Australasian College of Surgeons and the Melbourne media led to the Government of Victoria's becoming, on Friday, 22 December 1970, the first in the 'western' world to introduce legislation for this purpose (McDermott, 1978). Children under the age of 8 were excluded. The Government of New South Wales acted similarly in October 1971 and all other Australian states had followed by the end of January 1972. Additional legislation requiring that seat belts be fitted to older model motor vehicles was later introduced in all states. The percentage of Melbourne metropolitan drivers wearing seat belts increased from 15 per cent in the year before legislation to 65 per cent in 1973 and 90 per cent in 1977 (Vulcan, 1977; Road Safety and Traffic Authority of Victoria, 1978). The percentage for passengers was 4 per cent lower. In country areas the wearing rates have been approximately 10 per cent lower for both drivers and passengers. Comparable changes have occurred throughout Australia (Vaughan et al., 1974; McKenzie and Milne, 1976; Vaughan, 1977).

The hypothesis that seat belt wearing mitigates injury and improves survival prognosis for vehicle occupants involved in road crashes has been supported by previous Australian studies (Crinion et al., 1975; Trinca and Dooley, 1975; McDermott, 1978). Comprehensive road crash and injury data were obtained during 1971–3 in Victoria by the Royal Australasian College of Surgeons on 36 077 vehicle occupant casualties (Nelson, 1974). Analysis showed that casualties wearing seat belts had a lower probability of ejection, received fewer major or fatal injuries to the head and neck, trunk and upper extremities and had a lower probability of death (Nelson, 1974, 1977; Cameron and Nelson, 1977). The incidence of concussion, primary severe brain damage, intracranial compression and skull and facial fractures was significantly decreased in vehicle occupant casualties wearing seat belts (Cameron and Nelson, 1977). Cervical whiplash was the only injury with a significantly increased frequency in those wearing seat belts. The protection afforded by a seat belt appeared to be greater in frontal than in side impacts (Trinca and Dooley, 1975). Other studies have indicated a reduction in the incidence and severity of both spinal cord (Burke, 1977) and head injuries (Petty, 1975, 1977).

The protective value of seat belts is also supported by international experience. The enactment of legislation for compulsory wearing of seat belts has everywhere been followed by decreases in the incidence of vehicle occupant fatalities and injuries: in New Zealand the reduction was approximately 15 per cent (Toomath, 1977); in Sweden the number of road crash casualties admitted to 16 major hospitals was reduced by 29 per cent (Andreasson and Roos, 1977); and in France the occurrence of fatal injuries for front seat casualties was found to be approximately 65 per cent less than that found in those not wearing seat belts (Chodkiewicz and Dubarry, 1977). In Belgium compulsory seat belt wearing legislation was followed in the first 4 months by a 37 per cent reduction of fatalities and injuries (*British Medical Journal*, 1977). An analysis of 9000 front seat casualties in the United States, where seat belt wearing is not compulsory, showed that the incidence of severe or fatal injuries was reduced by about 65 per cent in those wearing seat belts (Huelke et al., 1977).

This paper examines changes in the incidence of road crash fatality and injury among vehicle occupants in Victoria and the rest of Australia for the period 1955–77. An evaluation is made of the significance of any altered trends after the introduction of legislation for compulsory wearing of seat belts.

Methods

Data

The annual numbers of road accident fatalities and injuries between 1955 and 1977 were obtained from the Australian Bureau of Statistics for motor vehicle occupants. For child passengers less than 8 years of age data were not available for 1955–6. Fatality and injury rates per 10 000 registered vehicles (motorcycles not included) were calculated for Victoria and for the rest of Australia (i.e. Australia minus Victoria).

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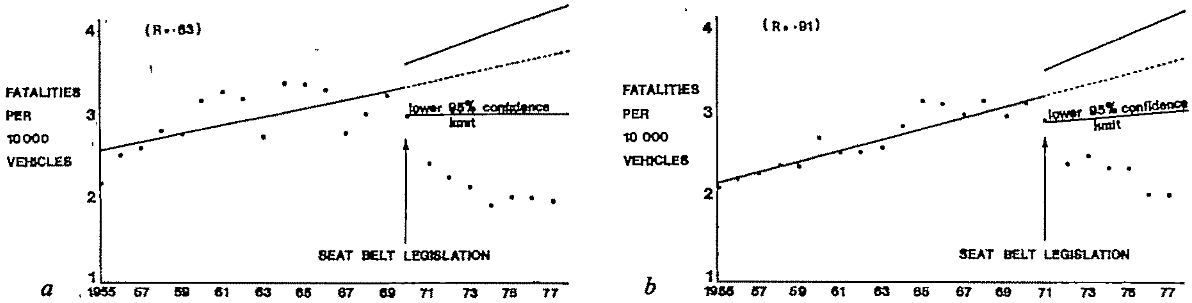

Fig. 1. Driver fatalities per 10 000 vehicles, 1955–77. *a*, Victoria; *b*, rest of Australia.

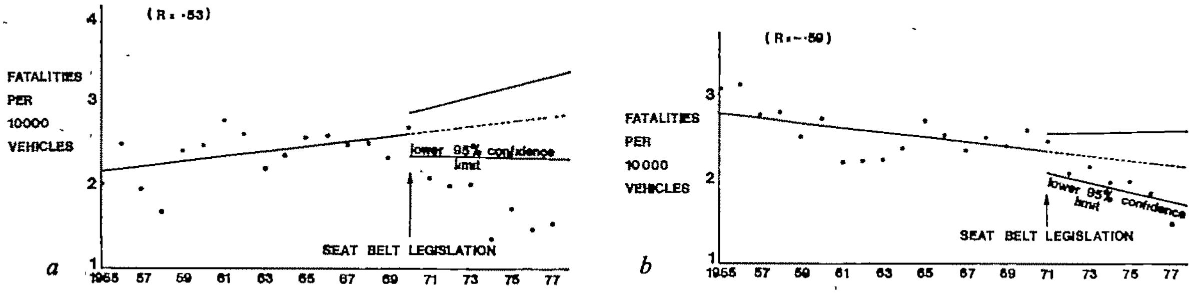

Fig. 2. Passenger fatalities per 10 000 vehicles, 1955–77. *a*, Victoria; *b*, rest of Australia.

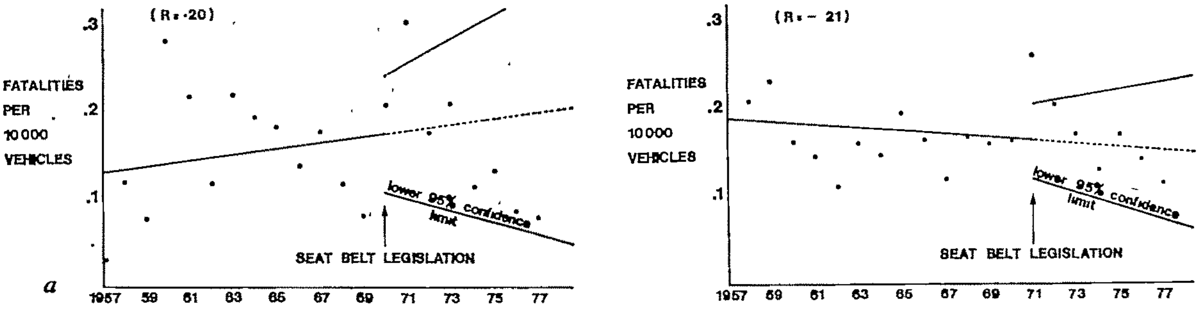

Fig. 3. Passenger fatalities among children under 8 years per 10 000 vehicles, 1957–77. *a*, Victoria; *b*, rest of Australia.

Table I: DRIVER FATALITIES AND INJURIES

	Pre-legislation correlation coefficient	No. of post-legislation years* (<lower 95% confidence limits)	Mann–Whitney U test
No. of fatalities			
Victoria	0·97	7/7	$P<0·01$
Rest of Australia	0·99	0/6	n.s.
No. of fatalities per 10^4 vehicles			
Victoria	0·63	7/7	$P<0·01$
Rest of Australia	0·91	6/6	$P<0·025$
No. of injuries			
Victoria	0·99	6/7	$P<0·01$
Rest of Australia	0·99	0/6	n.s.
No. of injuries per 10^4 vehicles			
Victoria	0·83	7/7	$P<0·01$
Rest of Australia	0·89	6/6	n.s.

* Post-legislation years: Victoria 1971–7; rest of Australia 1972–7.

Table II: PASSENGER FATALITIES AND INJURIES

	Pre-legislation correlation coefficient	No. of post-legislation years* (<lower 95% confidence limits)	Mann–Whitney U test
No. of fatalities			
Victoria	0·96	4/7	$P=0·01$
Rest of Australia	0·94	0/6	n.s.
No. of fatalities per 10^4 vehicles			
Victoria	0·53	7/7	$P<0·025$
Rest of Australia	−0·58	1/6	n.s.
No. of injuries			
Victoria	0·98	6/7	$P<0·01$
Rest of Australia	0·99	0/6	n.s.
No. of injuries per 10^4 vehicles			
Victoria	−0·39	7/7	$P=0·01$
Rest of Australia	−0·77	6/6	$P<0·05$

* Post-legislation years: Victoria 1971–7; rest of Australia 1972–7.

Table III: FATALITIES AND INJURIES AMONG CHILD PASSENGERS UNDER 8 YEARS OF AGE

	Pre-legislation correlation coefficient	No. of post-legislation years* (<lower 95% confidence limits)	Mann–Whitney U test
No. of fatalities			
Victoria	0·56	0/7	n.s.
Rest of Australia	0·70	0/6	$P<0{\cdot}05$
No. of fatalities per 10^4 vehicles			
Victoria	0·20	0/7	n.s.
Rest of Australia	−0·21	0/6	$P<0{\cdot}05$
No. of injuries			
Victoria	0·98	5/7	$P<0{\cdot}025$
Rest of Australia	0·97	0/6	n.s.
No. of injuries per 10^4 vehicles			
Victoria	0·47	7/7	$P<0{\cdot}01$
Rest of Australia	−0·18	1/6	n.s.

* Post-legislation years: Victoria 1971–7; rest of Australia 1972–7.

Statistical analysis

The significance of changes in the annual numbers of fatalities and injuries and in fatality and injury rates per 10 000 registered vehicles following the introduction of compulsory seat belt wearing have been evaluated by linear regression analysis and the non-parametric Mann–Whitney U test (Siegel, 1956).

Linear regression analysis: Pre-legislation data were subjected to linear regression analysis. The 95 per cent confidence limits were calculated and extrapolated for prediction of the range of expected post-legislation values.

Mann–Whitney U test: Differences in fatality and injury parameters between the sums of consecutive pairs of years were calculated. The differences of the first 4 post-legislation years (Victoria, 1971–4; rest of Australia, 1972–5) were compared with those before and after this period. Post-legislation differences which did not attain the 5 per cent level were considered non-significant.

Results

Driver fatalities and injuries

The results are summarized in *Table I.* Fatality and injury numbers and rates were less than predicted for each post-legislation year in Victoria. Post-legislation differences were reduced. Fatality and injury rates were also decreased for the rest of Australia. *Fig.* 1 shows the reduction in the fatality rates for Victoria and for the rest of Australia.

Passenger fatalities and injuries

The results are summarized in *Table II.* The numbers of passenger fatalities and injuries were decreased in Victoria. Fatality rates were decreased for Victoria for each post-legislation year but for only the last year in the rest of Australia (*Fig.* 2). Injury rates were decreased for all post-legislation years.

Child passenger fatalities and injuries

The results for children under the age of 8 are summarized in *Table III.* The numbers of fatalities and injuries were within predicted limits except for a decrease in injury numbers for the last 5 post-legislation years in Victoria. Fatality rates remained within the 95 per cent confidence limits (*Fig.* 3). Injury rates were decreased for each post-legislation year in Victoria but only for the last year in the rest of Australia.

Discussion

The introduction of legislation for compulsory wearing of seat belts in Victoria and subsequently in the other Australian states coincided with significant reductions in road fatalities and injuries among vehicle occupants. There have been no comparable changes for motorcyclists or pedestrians (Road Safety and Traffic Authority of Victoria, 1978). Despite increases in the number of registered vehicles, fuel consumption and population (Vulcan, 1977), the improvements have been maintained throughout the entire post-legislation period.

In Victoria and the other Australian states driver fatality and injury rates were shown by linear regression analysis to be significantly decreased. These decreases were enough to reduce the total numbers of driver fatalities and injuries for all post-legislation years in Victoria. Passenger fatality and injury rates were significantly reduced for all post-legislation years in Victoria. Except for the first post-legislation year, the total number of passenger injuries was also decreased for each post-legislation year. While the passenger injury rate for the rest of Australia was reduced, the decrease in fatality rate did not attain significance. The finding that reductions in fatality and injury were relatively less for passengers than for drivers may be related to their lower seat belt wearing rates.

The results of non-parametric statistical evaluation were in general agreement with those shown by linear regression analysis. In addition, significant decreases were demonstrated in the total number of passenger fatalities in Victoria and in the fatality rate and the total number of fatalities of child passengers under the age of 8 in the rest of Australia.

The reduction in vehicle occupant fatalities and injuries in Victoria was greater than in the rest of Australia and may be explained by additional factors operating in that state. These factors possibly include a maximum speed limit of 100 km/h introduced in 1974 and more comprehensive legislative countermeasures to drink–driving behaviour introduced in 1974 and 1976. An alteration in the criterion for police reporting of non-fatal injuries introduced in 1972 in Victoria is believed to account for part of the reduction in that state.

Legislation for compulsory wearing of seat belts had not applied to child passengers of less than 8 years of age. As a consequence the frequency of seat belt or harness wearing for child passengers remained low (Boughton et al., 1977; King, 1977). These children did not share in the overall improvement for passengers. The fatality rate for 0–7-year-olds was not reduced although differences attained significance for the rest of Australia. There has, however, been a reduction in non-fatal injuries, albeit smaller than that for the total passenger group. The injury rate was less than predicted for all post-legislation years in Victoria and for 1977 in the rest of Australia. The total number of injuries was also reduced in Victoria for the last 5 years of the post-legislation period. These improvements may be partly explained by legislation introduced in Victoria in 1975 making seat belt or harness wearing compulsory for children occupying front seats and subsequent legislation in New South Wales and Western Australia applied to all children. There is an urgent need for the further development and evaluation of child restraint systems and for an extension of compulsory seat belt wearing legislation throughout Australia to all child passengers.

Experience in Victoria and the other Australian states supports the hypothesis that seat belt wearing reduces the likelihood of injury to vehicle occupants involved in road crashes and increases the prognosis for survival. Legislation for compulsory wearing of seat belts remains the single most effective measure available for the protection of vehicle occupants in road crashes.

The benefit of legislation for compulsory wearing of seat belts would be increased by greater public compliance. Surveys in Victoria (Nelson, 1974) and Western Australia (Court, 1977) have shown that the frequency of seat belt wearing in vehicle occupants involved in road crashes is less than that of sample populations. Between 1972 and 1975 in Western Australia, police attended 25 948 road crashes involving 67 687 casualties. The seat belt wearing rates among fatal and non-fatal casualties were only 30 per cent and 37 per cent, respectively. Of vehicle occupants not wearing seat belts, 2·3 per cent were killed and 40 per cent injured. On the other hand, only 0·7 per cent of those wearing seat belts sustained fatal injuries and 16 per cent non-fatal injuries.

The results presented support the view that governments that enact legislation making seat belt use compulsory are reducing the risk of fatality and injury for vehicle occupants involved in road crashes.

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References

ANDREASSON R. and ROOS K. (1977) Effects of Sweden's seat belt laws. In: *Proceedings of the Sixth International Conference of the International Association for Accident and Traffic Medicine, Melbourne, 31 January to 4 February 1977.* International Association for Accident and Traffic Medicine, pp. 45–55.

BOUGHTON C. J., LANCASHIRE B. R. and JOHNSTON I. R. (1977) Child restraint usage in Melbourne and Canberra: evaluation of Victorian legislation. In: *Proceedings of the Sixth International Conference of the International Association for Accident and Traffic Medicine, Melbourne, 31 January to 4 February 1977.* IAATM, pp. 284–298.

BRITISH MEDICAL JOURNAL (1977) Parliament. Seat belts Bill defeated. 1, 1225.

BURKE D. C. (1977) Spinal cord injuries, 1976. *Aust. NZ J. Surg.* 47, 166–170.

CAMERON M. H. and NELSON P. G. (1977) Injury patterns with and without seat belts. In: *Proceedings of the Sixth International Conference of the International Association for Accident and Traffic Medicine, Melbourne, 31 January to 4 February 1977.* IAATM, pp. 423–479.

CHODKIEWICZ J. P. and DUBARRY B. (1977) Effects of mandatory seat belt legislation in France. In: *Proceedings of the Sixth International Conference of the International Association for Accident and Traffic Medicine, Melbourne, 31 January to 4 February 1977.* IAATM, pp. 40–44.

COURT R. J. (1977) Compulsory seat belt wearing in Western Australia. In: *Proceedings of the Sixth International Conference of the International Association for Accident and Traffic Medicine, Melbourne, 31 January to 4 February 1977.* IATTM, pp. 130–141.

CRINION J. D., FOLDVARY L. A. and LANE J. C. (1975) The effect on casualties of a compulsory seat belt wearing law in South Australia. *Accident Anal. Prev.* 7, 81–89.

HUELKE D. F., LAWSON T. E., SCOTT R. et al. (1977) The effectiveness of belt systems in frontal and rollover crashes. In: *Proceedings of the Sixth International Conference of the International Association for Accident and Traffic Medicine, Melbourne, 31 January to 4 February 1977.* IAATM, pp. 168–203.

KING K. L. (1977) Queensland survey on the installation of child restraints. In: *Proceedings of the Sixth International Conference of the International Association for Accident and Traffic Medicine, Melbourne, 31 January to 4 February 1977.* IAATM, pp. 345–350.

MCDERMOTT F. T. (1978) Control of road trauma epidemic in Australia. *Ann. R. Coll. Surg. Engl.* (In the press.)

MCKENZIE J. A. and MILNE P. W. (1976) Seat belt fitting and wearing in Australia. Seat Belt Seminar, Melbourne, 9–11 March 1976, Paper No. 1. Department of Transport.

NELSON P. G. (1974) *Pattern of Injury Survey of Automobile Accidents, Victoria, Australia, June 1971 to June 1973.* Melbourne, Royal Australasian College of Surgeons. Road Trauma Committee.

NELSON P. G. (1977) Aspects of injury patterns in automobile accidents. *Aust NZ J. Surg.* 47, 162–165.

PETTY P. G. (1975) The influence of seat belt wearing on the incidence of severe head injury. *Med. J. Aust.* 2, 768–769.

PETTY P. G. (1977) The influence of seat belt wearing on the incidence of severe head injury. In: *Proceedings of the Sixth International Conference of the International Association for Accident and Traffic Medicine, Melbourne, 31 January to 4 February 1977.* IAATM, pp. 489–493.

ROAD SAFETY AND TRAFFIC AUTHORITY OF VICTORIA (1978) Data.

SIEGEL S. (1956) *Nonparametric Statistics in the Behavioural Sciences.* New York, McGraw-Hill, pp. 116–127.

TOOMATH J. B. (1977) Compulsory seat belt legislation in New Zealand. In: *Proceedings of the Sixth International Conference of the International Association for Accident and Traffic Medicine, Melbourne, 31 January to 4 February 1977.* IAATM, pp. 21–39.

TRINCA G. W. and DOOLEY B. J. (1975) The effects of mandatory seat belt wearing on the mortality and pattern of injury of car occupants involved in motor vehicle crashes in Victoria. *Med. J. Aust.* 1, 675–678.

VAUGHAN R. G. (1977) Seat belts—some aspects of compulsory wearing in New South Wales, Australia. *Proc. Inst. Mech. Eng. (Automobile Division)* 191, 31–38.

VAUGHAN R. G., WOOD R. and CROFT P. G. (1974) Some aspects of compulsory seat belt wearing. In: *Proceedings of the 7th Australian Road Research Board Conference, Adelaide, 1974.* 7, pp. 103–124.

VULCAN A. P. (1977) Victorian experience with the compulsory wearing of seat belts. In: *Proceedings of the Sixth International Conference of the International Association for Accident and Traffic Medicine, Melbourne, 31 January to 4 February 1977.* IAATM, pp. 99–114.

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Br. J. Surg. Vol. 66 (1979) 522–523

A study of basal cell carcinoma of the inner canthus, 1967–72

JOHN C. McGREGOR*

SUMMARY

Basal cell carcinoma was the commonest malignant lesion at the inner canthus. Reconstruction following excision was most commonly achieved with a post-auricular full thickness graft. Provided excision is adequate, a local flap is a good alternative. There is no evidence that the use of a graft increased recurrence, but it may have allowed earlier detection. The primary recurrence rate after primary surgical excision was 3·6 per cent. Recurrence occurred in several cases when histology indicated incomplete excision. Follow-up under these circumstances should be continued for up to 10 years. When adequate primary surgical excision was performed, there was no evidence that rodent ulcer of the inner canthus behaves differently or has a worse prognosis than at other sites. There has probably been undue concern in the past about epiphora following resection of the lacrimal drainage system.

RODENT ulcer at the inner canthus has a sinister reputation (Bennett, 1974). However, there have been no reports to suggest the prognosis is any worse than elsewhere. There has also been debate regarding the best method of reconstruction following excision. Hirshowitz and Mahler (1971) have suggested that repair with grafts rather than flaps is more satisfactory in order to allow earlier detection of recurrence. Taylor and Barisoni (1973), on the other hand, suggested that the use of grafts was associated with an increased incidence of recurrence.

For these reasons, it was decided to carry out a retrospective study of lesions of the inner canthus treated at Canniesburn Hospital over the period 1967–72. Forty-one males and 46 female patients with a total of 88 rodent ulcers were recorded. The age range was 24–81 years (maximum incidence 5th and 6th decades). The average diameter was 0·97 cm (range 0 3–2·0 cm). In 7 males and 1 female basal cell carcinomas were or had been present at other sites.

Patients and methods

Management

General anaesthesia was employed in 75 of the rodent ulcers. The remainder were excised under local anaesthesia. The majority of the defects following excision were repaired with post-auricular full thickness grafts and the remainder by a variety of local flaps or direct closure (*Table I*). The glabellar flap was the most commonly used flap. The puncta were involved in 7 patients and an attempt to reconstruct the drainage system, using silicone tubing or nylon sutures, was made in 2 cases.

In all but one case comment was made on the completeness of excision. The limits were definitely involved in 13 and possibly so in 4 cases. Eight were reported as multifocal rodent ulcers.

Recurrence

A recurrence rate of 3·6 per cent (2 females, 1 male) was recorded in those having primary surgery in the series. In all these the defect had been grafted. Pathology revealed incomplete excision at the deep margin in 2 cases and at the lateral margin in one other case. The recurrences presented 2, 4 and 7 years after initial surgery. Two have been clear of further recurrence for 1 and 4 years respectively; the third has so far required four re-excisions.

Table I: METHODS OF REPAIR FOLLOWING EXCISION OF RODENT ULCERS OF THE INNER CANTHUS

	Male	Female	Total
Direct closure	2	4	6
Skin graft			
Split	1	0	1
PAWG	26	23	49
Supraclavicular	2	0	2
Nasolabial	1	0	1
Flap			
Glabellar	4	9	13
Eyelid	2	4	6
Cheek or forehead	3	2	5
Unspecified	1	4	5

There were 8 male and 1 female patients who had primary treatment elsewhere. In 2, the nature of the previous treatment was unrecorded; in 2, surgical excision had been performed 7 and 9 years prior to recurrence. In the remaining 5 patients, the recurrence occurred from 6 months to 5 years after radiotherapy. Following secondary surgery, the limits of excision were reported as clear. No further recurrence has been reported (follow-up 2–4 years).

Complications following surgery

Epiphora was reported in 8 cases, but in 3 it was transient. The repair had been with a graft in 3 cases; in the remainder, a flap had been used. The puncta or nasolacrimal system had been excised in 5 cases with an attempt at reconstruction in 2 cases. In no case was the epiphora described as being severe or incapacitating.

Ectropion was recorded in 6 cases, but in 4 it was transient. Flap repair had been used in 2 cases, grafts were used in the remainder. Ectropion and epiphora occurred together in 3 cases.

Discussion

Basal cell carcinoma was found to be the most common skin lesion requiring excision at the inner canthus. In the majority of cases operation was performed under general anaesthesia and reconstruction in 60·9 per cent was with post-auricular full thickness grafts. There was no evidence that this increased the risk of recurrence, but it would appear that the use of a graft allows earlier detection of a recurrence (Hirshowitz and Mahler, 1971). A graft may therefore be a wise choice for the inexperienced surgeon or where there is doubt as to the adequacy of clearance. Adequate excision under good operative conditions should precede reconstruction of any kind. Failure to achieve this may account in part for the bad reputation of rodent ulcers at the inner canthus. The recurrence rate in this series (3·0 per cent) is very similar to recurrence rates for surgically treated rodent ulcers at other sites (3·0 per cent) (Hayes, 1962). It would seem that recurrence is more likely if

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excision was incomplete histologically and there may be a relatively long latent period before recurrence becomes evident. Follow-up should be maintained in these cases for at least 10 years. An alternative approach would be to re-operate at an early stage if a report which suggests inadequate excision is obtained. It should be noted, however, that of 17 lesions with an unsatisfactory histological report there have so far been only 3 cases of recurrence. This would indicate that close follow-up rather than immediate re-excision can be acceptable. Similar observations have been made by Pascal et al. (1968) and Golwyn and Kasdon (1978).

Complications following surgery were uncommon. None of the patients has died as a result or from recurrence. None has required exenteration of the orbit. The incidence of epiphora was 9 per cent and appeared to persist in cases where the upper and lower puncta had been excised. In none was the epiphora a problem. Thus, surgical excision of an inner canthal rodent ulcer should not be compromised because of the proximity of this structure. It is debatable whether reconstruction of the nasolacrimal system is absolutely necessary.

Acknowledgements

I am grateful to the consultant plastic surgeons in Canniesburn Hospital for allowing me to study their cases. I would also like to thank Nancy Halleran for obtaining the case records and Evelyn Cruikshank for typing the manuscript.

References

BENNETT J. P. (1974) From noli-me-tangere to rodent ulcer: the recognition of basal cell carcinoma. *Br. J. Plast. Surg.* **27**, 144–154.

GOLWYN R. M. and KASDON E. J. (1978) The 'disappearance' of residual basal cell carcinoma of the skin. *Ann. Plast. Surg.* **1**, 286–289.

HAYES H. (1962) Basal cell carcinoma: the East Grinstead experience. *Plast. Reconstr. Surg.* **30**, 273–280.

HIRSHOWITZ B. and MAHLER D. (1971) Incurable recurrences of basal cell carcinoma of the mid face following radiation therapy. *Br. J. Plast. Surg.* **24**, 205–211.

PASCAL R. R., HOBBY L. W., LATTES R. et al. (1968) Prognosis of 'incompletely excised' versus 'completely excised' basal cell carcinoma. *Plast. Reconstr. Surg.* **41**, 328–332.

TAYLOR G. A. and BARISONI D. (1973) Ten years experience in the surgical treatment of basal cell carcinoma: a study of factors associated with recurrence. *Br. J. Surg.* **60**, 522–529.

Paper accepted 6 November 1978.

Book reviews

Modern Perspectives in the Psychiatric Aspects of Surgery

Edited John G. Howells. 240 × 150 mm. Pp. 756. 1978. London: Macmillan. £15·00.

NOT many surgeons will read or refer to this book and in many ways that will be a pity. However, their reluctance may be reinforced by the fact that the book largely comprises psychiatrists' observations on surgery and surgical patients—of its 48 contributors, 34 are psychiatrists (one of them with a surgical fellowship), 5 physicians, 4 psychologists, just 3 (I think) surgeons, 1 dentist and 1 anaesthetist. Perhaps this tells us something about surgeons who, though often sympathetic and warm, are rarely analytic about their patients' mental state or receptive in the formal sense to cries of help from minds in torment. Nevertheless, it seems a pity that psychiatrists have not entered more often into partnerships with surgeons nor savoured a little bit more the views and opinions of those actually involved in surgical care. It would, I believe, have rendered their accounts a little less wordy and sometimes even their conclusions a little more rounded. In particular I find it difficult to see why a physician should write the opening chapter on the ethical objectives of surgery: Dr A. Paton's account is as good as one would expect from him but it clearly does not reflect a deep and intuitive understanding of what makes surgeons 'tick' or the objectives they pursue.

In spite of these general observations, the work is a mine of information for anyone who seeks an entry point into the still largely unmapped terrain of the psychological and social aspects of surgical illness. The historical reviews are for the most part excellent. The bibliography seems to end about 1974 which possibly accounts for a rather superficial account of postoperative delirium and an absence of the recent important work of Devlin and his colleagues on colostomy and ileostomy. These are areas of which I can claim some knowledge and they set one wondering if the same is possibly true of other sections. The production is excellent and the index and referencing exemplary. Definitely a volume for the library shelf and the personal possession of all those particularly concerned with this fascinating interdisciplinary field.

H. A. F. DUDLEY

Gynaecology

Langdon Parsons and Sheldon C. Sommers. Second edition. 270 × 185 mm. Pp. 1660+xxxii. Illustrated. 1978. Eastbourne: Holt–Saunders. £35·00.

THE second edition of this well-established American textbook follows 16 years after the first, and presents the carefully weighed opinions of an emeritus professor of gynaecology and of a professor of pathology. Its approach is thus comprehensive yet conservative and its constant references to pathology give it a diagnostic rather than therapeutic bias.

The arrangement of the sections into the 'ages of woman' is interesting although at times artificial, but the paragraph headings in the form of questions help to hold the reader's attention. In fact the book as a whole is a joy to read and a model of lucid prose.

Should this rather expensive volume of almost 1700 pages find a place on the surgeon's bookshelf? It will not assist him in deciding on the operative management of female surgical patients, but if he is looking for a thorough and thoughtful review of current thinking in gynaecology he will be rewarded. There are certain areas where British and American practices differ (bromocriptine and danazol are barely given a mention), but the very comprehensive references up to 1976 help to make up for any apparent deficiencies in the text. Printing errors are confined to several authors' names in the references and to the unfortunate transposition of the legend to the illustrations of methods of sterilization in *Fig.* 30–5.

D. H. HORWELL

Cancer in China

Edited H. S. Kaplan and P. J. Tsuchitani. 220 × 150 mm. Pp. 240 +xii, with 34 illustrations. 1978. New York: Alan R. Liss Inc. No price given.

WHILE the problems of cancer remain largely unsolved all of us are curious about the work of others. *Cancer in China* appeals to one's curiosity on two scores: first, because it is about cancer and, to a secondary degree, because it is also about modern China itself.

The volume is a report of a visit to the People's Republic of China by a delegation of ten American scientists, a China scholar specializing in geography and a staff officer.

The book starts by detailing the organization of medical care in China and then goes on to describe the cancer research institutes, hospitals and medical colleges visited. The section on epidemiology is of interest, giving tables of occurrence of cancer at different sites and comparing these with figures for the UK and America. The three great Chinese cancer problems, namely nasopharyngeal, oesophageal and liver cancer, are dealt with fully. Comparative methods of early diagnosis and treatment by surgery, radiation therapy and chemotherapy are discussed.

No one would claim that this book gives us a full picture of all that the Chinese know about cancer, but as an edited diary of this group's visit, it makes interesting reading.

G. J. HADFIELD

Radiological Atlas of Biliary and Pancreatic Disease

H. Baddeley, D. J. Nolan, and P. R. Salmon. 260 × 200 mm. Pp. 256, with 297 illustrations. 1978. Aylesbury: H M+M.

THIS compact book sets out to provide an atlas of the radiological appearances of biliary and pancreatic disease. It is timely, since it illustrates beautifully the newer techniques of endoscopic retrograde choledochopancreatography and of fine needle percutaneous cholangiography. The illustrations are of a very high calibre and cover a wide range of conditions, depicting even minor variations in anatomy and in disease. There are few criticisms of the illustrations but one on p. 69 (*Fig.* 6.46) should be omitted since it has not reproduced well and is open to alternative interpretation. The vexed question of papillary stenosis is dealt with and convincing pictures produced of secondary stenotic lesions. However, as in so many other publications, the evidence for primary biliary stenosis and biliary dyskinesia is unconvincing.

The illustrations of the pancreatic duct are of a very high order and are especially valuable in outlining anatomical variations and minor degrees of pancreatic damage seen in chronic pancreatitis.

This book, whilst highly successful as an atlas, does not quite succeed in its second stated aim, namely 'to suggest patterns of investigation which we hope will be of use to radiologists, physicians and surgeons'. There is perhaps too much emphasis on ERCP and less on other methods of investigation and especially ultrasonic display of abnormalities of the biliary tree and pancreas. This is particularly evident in some of the discussions relating to the pancreas and pancreatic cysts. It should perhaps not be expected that an atlas deal fully with complications of investigations or their ordered use, but perhaps some of the dangers inherent in the use of ERCP in acute pancreatitis could have been more fully stated and the real contribution which can be made by less invasive means emphasized.

Despite these minor criticisms, this book fulfils an important role and should find a place on the shelves of all those interested in the niceties of biliary and pancreatic diagnosis and treatment. I concur with the final sentence of the Foreword that the book should be in the library of all centres undertaking the training of radiologists.

L. BLUMGART

Recent Publication

SURGICAL PROBLEMS IN THE AGED

Edited by K. D. J. VOWLES, MB, CHB, FRCS,
Consultant Surgeon, Devon and Exeter Clinical Area

Contents: Foreword by Sir Ferguson Anderson; Surgery for the Aged; Assessment before Surgery; Anaesthesia for the Aged; The Problem of Dysphagia; Gastroduodenal Problems; Biliary Tract and Pancreatic Problems; Problems with Hernia, the Small Intestine and the Appendix; Colonic and Rectal Problems; Urological Problems; Problems of the Aged Hip; Vascular Problems and the Aged Amputee; Postoperative Problems in the Aged; Index.

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July Publication

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H. P. HENDERSON, FRCS, *Senior Registrar, Plastic and Jaw Surgery, Fulwood Hospital, Sheffield;* and M. J. KELLY, MChir, FRCS, MRCP, *Senior Registrar in General Surgery, Bristol Royal Infirmary*

With a Foreword by The Right Hon. the Lord Smith of Marlow, KBE, MS, FRCS

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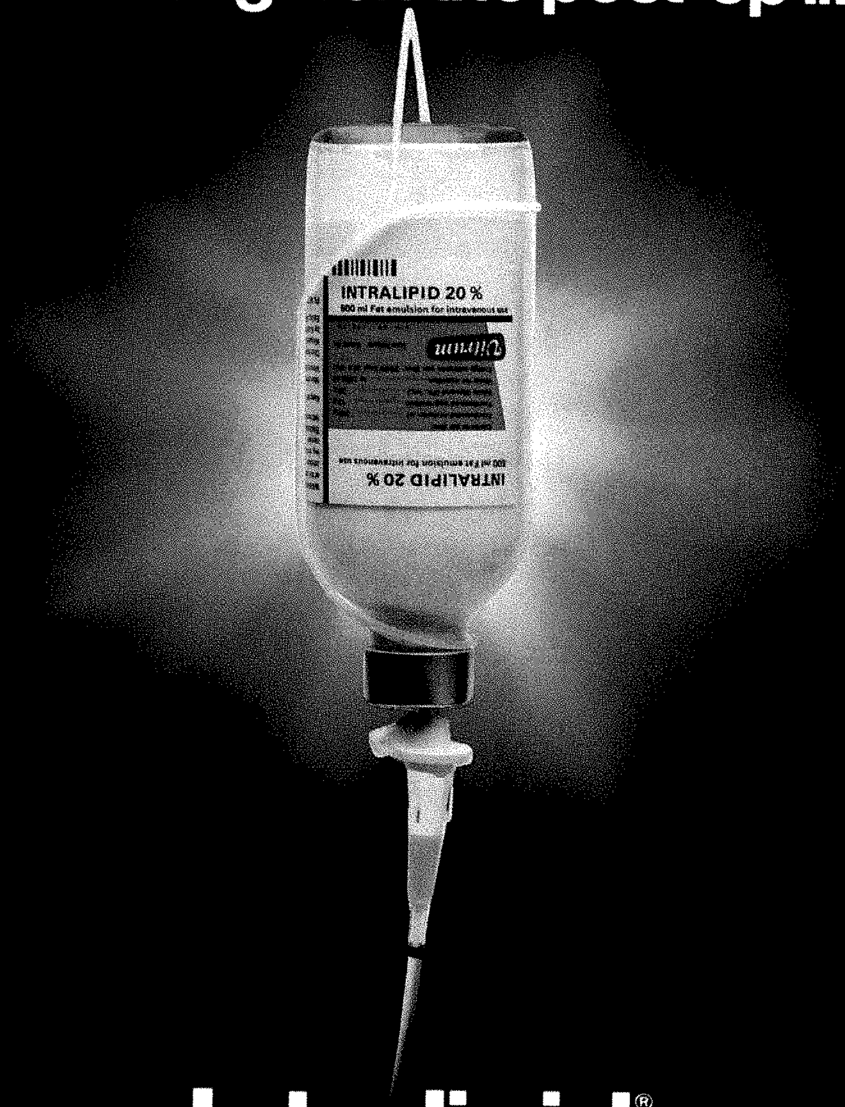
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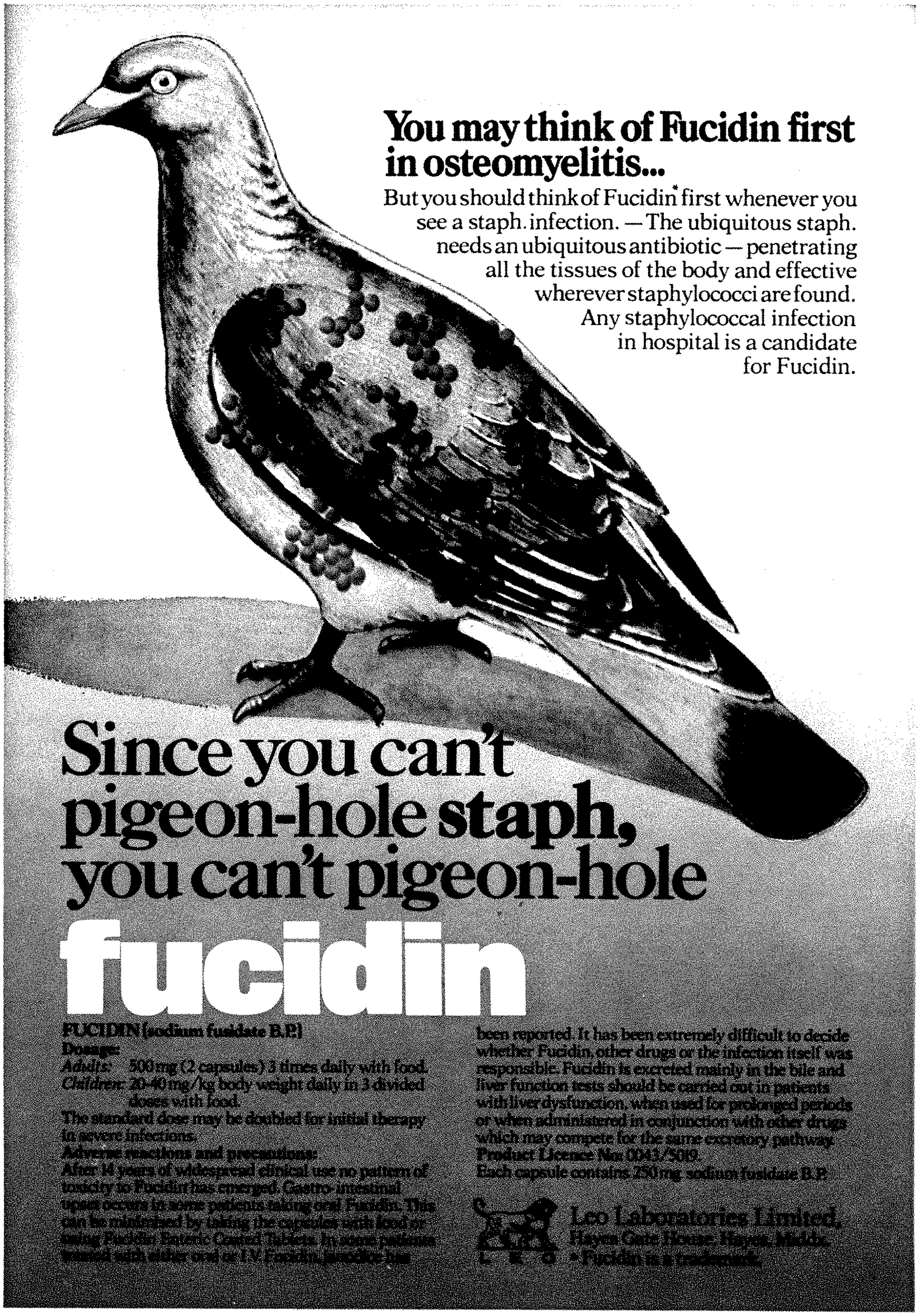

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(Study of 40 patients given Danol for up to 6 months. Obstet. Gynec. 1976, 48: 93.)

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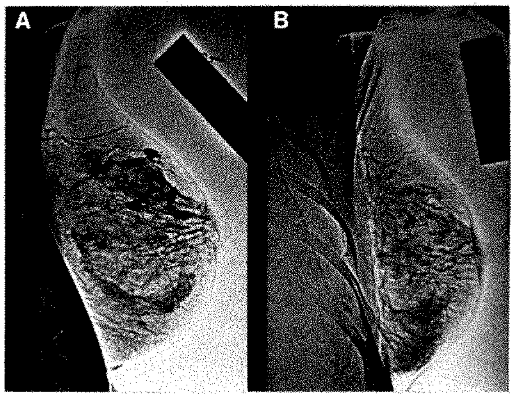

Xeromammograms of patient with intense fibrocystic disease (A) showing marked reduction in breast size and cystic area (B) after 6 months on Danol.

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3. "..a significant decrease and elimination of breast pain and tenderness ...and elimination of nodules and lumpy areas..."

(Preliminary report on open study of 260 patients given Danol for 4 to 6 months. J. int. med. Res. 1977, 5 (Suppl. 3) 101-108.)

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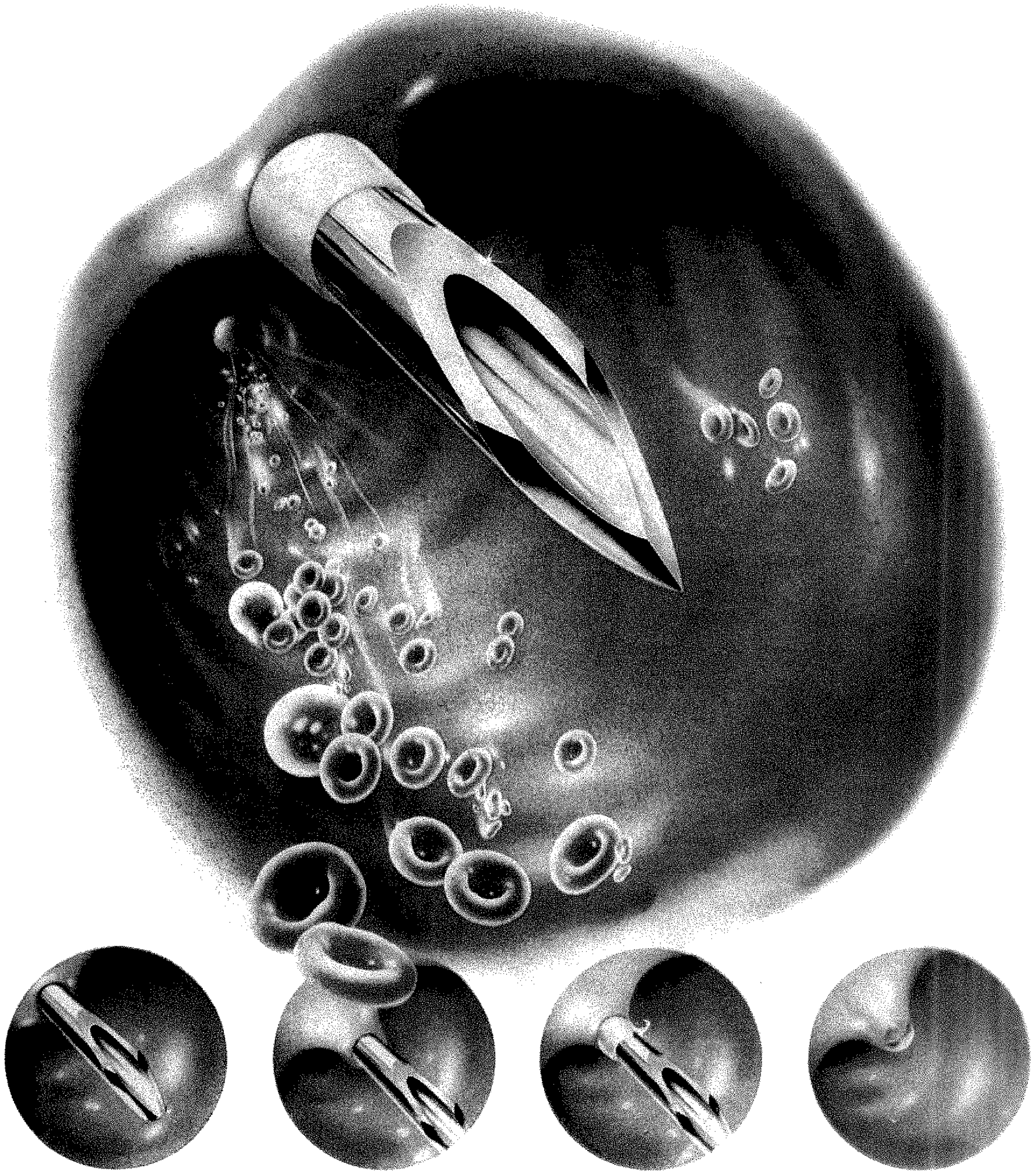

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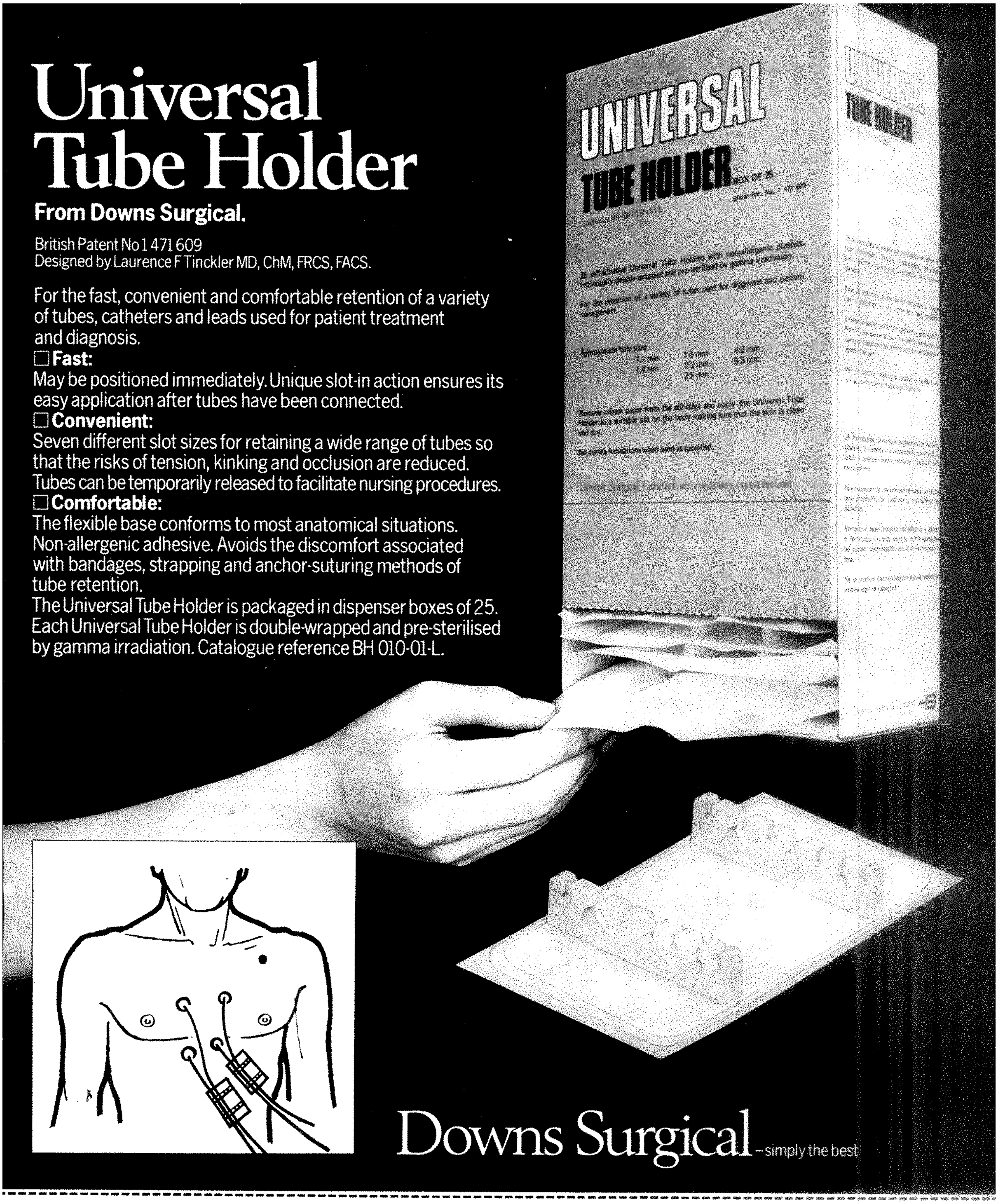

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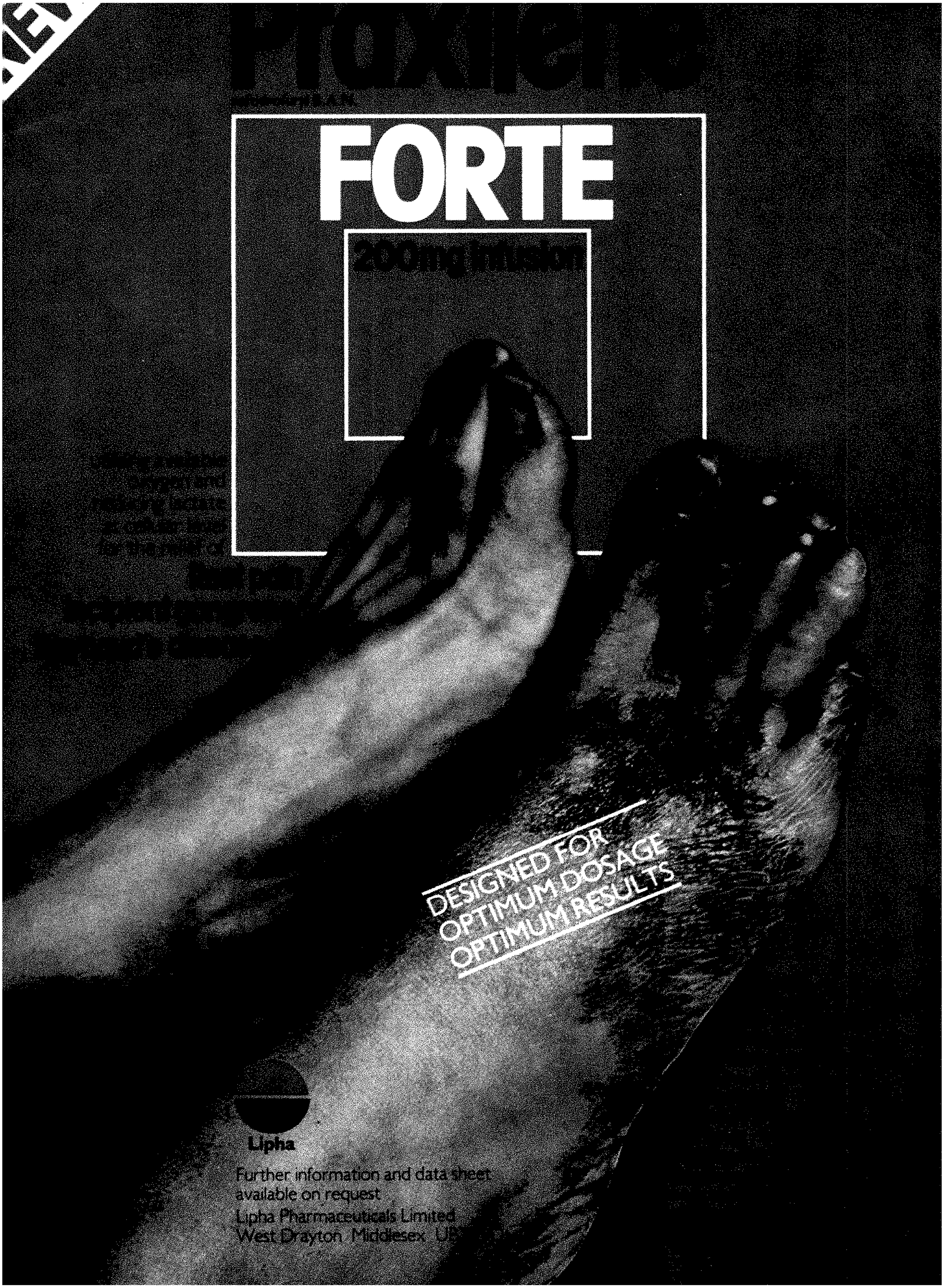

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The management of gross refractory obesity by jejuno-ileal bypass

R. M. BADDELEY†

SUMMARY

Jejuno-ileal bypass has been performed in 226 massively obese patients, 190 of whom have been followed for a minimum of 1 year. End-to-side and end-to-end anastomoses were compared and no difference in the weight reduction achieved by either technique was seen throughout the 5-year follow-up. There was no significant difference in weight reduction achieved between groups of patients in which the jejunal length varied from 10 to 35 cm and the ileal length from 35 to 10 cm.

The weight reduction achieved in the entire series averaged 36·7 ± 9·4 per cent at 2 years, after which no further loss occurred. Good psychological benefits were recorded. Remission of diabetes occurred in 12 of 13 patients and marked long term lowering of serum lipids was seen.

Side effects included fluid and electrolyte disturbances and fatty changes in the liver during the first year, improving thereafter. Early cirrhosis of the liver occurred in 8·6 per cent. Other side effects included abdominal bloating, arthralgia and renal colic.

The operative mortality was 0·9 per cent and the late mortality directly attributable to the jejuno-ileal bypass, 3·1 per cent. In 19 patients the bypass was discontinued because of severe side effects.

THE use of small bowel bypass in the management of gross obesity was first reported by Kremen, Linner and Nelson in 1954. Later, Payne and DeWind (1969) found optimal results with 14 in (35 cm) of jejunum anastomosed end-to-side to the terminal ileum 4 in (10 cm) from the ileocaecal valve. Subsequently, other surgeons have varied the lengths of jejunum and of ileum and some have used an end-to-end anastomosis.

In the present series 226 massively obese patients have undergone jejuno-ileal bypass, 190 of them having a minimum follow-up of 1 year. The age range was 16–60 years; there were only 26 males. The criteria for acceptance for the procedure were (*a*) chronic simple obesity of at least 5 years' duration, which had (*b*) proved refractory to properly supervised dietary measures, and which (*c*) amounted to at least 45 kg or 100 per cent above standard body weight for age, sex and height.

Methods

Preoperative assessment

Preoperative investigations were designed to confirm the gross simple nature of the problem by screening for rare endocrine causes such as Cushing's disease and myxoedema, to expose subclinical abnormalities such as diabetes, hyperlipidaemia and deficiency states and to provide baselines for postoperative comparison. In addition, percutaneous liver biopsy was performed when biochemical liver function tests were abnormal.

Surgical techniques

Each patient received conventional bowel preparation and prophylactic antithrombotic therapy. Midline incision was preferred to paramedian or transverse incisions to minimize the duration of the operation. Liver biopsies were taken routinely and gallstones, hiatus hernia and pelvic abnormalities sought. Details of the technique of jejuno-ileal bypass have been described elsewhere (Baddeley, 1977).

Postoperative management

The management of postoperative ileus followed conventional lines of nasogastric suction and intravenous fluids. Profuse diarrhoea started by the third or fourth day but this was satisfactorily controlled with Lomotil (5 mg four times daily) and restriction of oral fluids to 1200–1500 ml daily). An oral potassium preparation was routinely prescribed.

In recent years all post-bypass patients have been placed on a high protein, low fat, low calorie diet of up to 1500 kcal daily. The low fat content lessens the problem of diarrhoea and the high protein intake is aimed at achieving an appropriate protein–calorie balance.

After discharge from hospital most patients have been reviewed regularly and haematological and biochemical profiles obtained. Annual liver and bone biopsies have been performed.

Results

End-to-side v. *end-to-end jejuno-ileal bypass*

The majority of surgeons reporting their experience with jejuno-ileal bypass have found considerable variation in the amount of weight loss achieved. This inconsistency has been attributed by some to reflux of bowel contents into the excluded ileum thereby providing a greater absorptive surface. They have sought to prevent it by end-to-end jejuno-ileal anastomosis, implanting the excluded ileum into the ascending, transverse or sigmoid colon. Scott et al. (1977) reported greater and more consistent weight loss using this technique.

In 1972 this study was commenced to compare the efficacy of the two types of anastomosis. Two groups of patients were randomly assigned to one or other

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* Based on a Hunterian Lecture given to the Royal College of Surgeons meeting at Birmingham, 24 February 1978.

† The General Hospital, Steelhouse Lane, Birmingham.

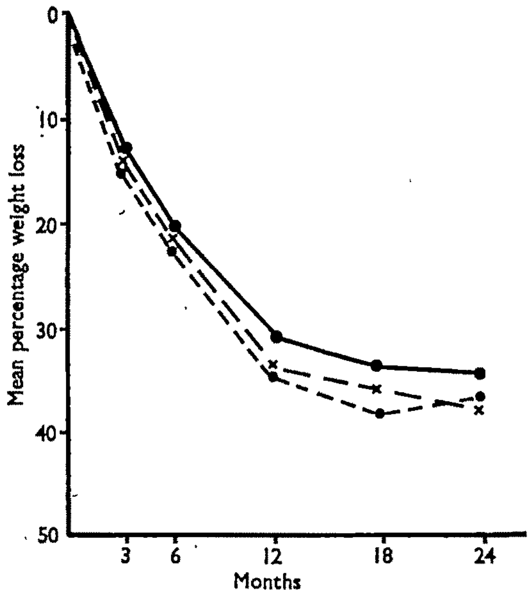


Fig. 1. Comparison of three sizes of jejuno-ileal bypass. ●——●, 35 cm of jejunum and 10 cm of ileum ($n = 18$); ×——×, 30 cm of jejunum and 15 cm of ileum ($n = 14$); ● - - - ●, 30 cm of jejunum and 10 cm of ileum ($n = 17$). P value not significant at any stage between any groups of patients.

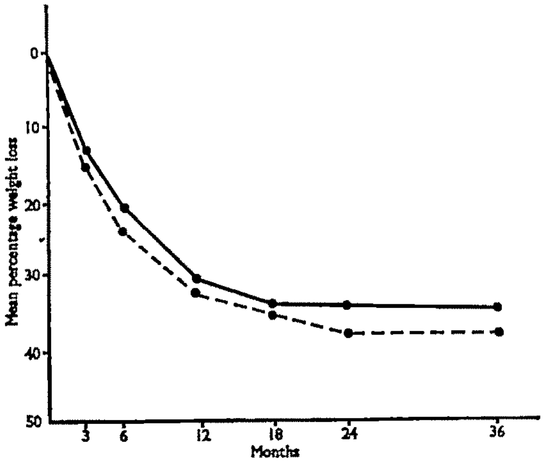


Fig. 2. Comparison of long jejunal segment and long ileal segment jejuno-ileostomy. ●——●, 35 cm of jejunum and 10 cm of ileum ($n = 18$); ● - - - ●, 10 cm of jejunum and 35 cm of ileum ($n = 16$). P value was not significant at any stage.

Table I: MEAN PERCENTAGE WEIGHT LOSS AFTER TWO TYPES OF JEJUNO-ILEOSTOMY

Time (mth)	End-to-side	End-to-end
3	14·2	16·2
6	21·5	23·4
12	31·3	33·6
18	36·2	36·8
24	39·5	37·8
36	37·3	36·0
48	37·8	36·2
60	38·2	36·6

procedure, the lengths of jejunum and ileum retained in enteric continuity being 35 cm of jejunum and 10 cm of ileum in both. The groups were comparable for age, sex and original weight. No significant difference in weight loss was seen during the entire 5-year period of follow-up (*Table I*). The incidence of side-effects was similar in both groups.

These findings conflict with those of Scott et al. (1977) but agree with Gaspar et al. (1976) and Merscheimer et al. (1977). Recently, pneumatosis cystoides intestinalis and bypass enteritis (Passaro et al., 1976) have been reported in patients who had undergone end-to-end jejuno-ileostomy and ileosigmoidostomy. For this reason, and because end-to-side jejuno-ileostomy is a simpler and quicker method, the latter procedure has been preferred since 1973.

Optimal lengths of jejunum and ileum

The lengths of jejunum and ileum retained in continuity are of importance as too much retained bowel results in inadequate weight loss and too little bears the risk of serious nutritional deficiencies. The early clinical studies of Payne and DeWind (1969) suggested that 35 cm of jejunum and 10 cm of ileum gave optimal weight reduction with minimal hazards but some surgeons have subsequently varied these measurements to achieve better and more consistent weight reduction. These variations have been from as much as 40 cm to as little as 10 cm of jejunum and from 50 cm to as little as 4 cm of ileum.

Scott et al. (1977) compared groups of patients in whom bypasses consisted of 30 cm of jejunum but the ileal lengths were variously 30 cm, 20 cm and 15 cm. They concluded that the optimal lengths were 30 cm of jejunum and 20 cm of ileum, shorter lengths being associated with more diarrhoea and metabolic difficulties.

To evaluate further the optimal lengths of small bowel retained in continuity, consecutive patients in this series were allocated randomly to jejuno-ileal end-to-side bypass procedures in which the lengths of jejunum were 35 cm, 30 cm or 10 cm and the lengths of ileum were 10 cm, 15 cm or 35 cm respectively. The percentage weight reduction achieved in each group of patients is shown in *Fig.* 1 which reveals no significant difference between any combination of these dimensions. The incidence of side effects was similar in each. Short lengths of jejunum (10 cm) with long lengths of ileum (35 cm) induced no significant improvement in weight loss than the reverse measurements (*Fig.* 2).

The total length of small bowel in continuity is of importance. Jejuno-ileum measuring 70 cm is associated with little or no weight reduction. Patients with 47 cm of jejuno-ileum lose significantly more weight than those with 50 cm (Baden, 1974; Quaade, 1977). The optimal length of jejuno-ileal bypass thus probably lies between 45 and 50 cm. In view of the importance of balanced protein–calorie nutrition, it may be judicious to retain a longer length of jejunum than of ileum for nutrient absorption and thus the measurements 30 cm of jejunum and 20 cm of ileum are used at present.

Pattern of weight reduction

There being no significant difference in the weight reduction achieved by varying the lengths of small bowel or the type of anastomosis, the results in all groups have been compiled and presented as a pattern of weight reduction in *Fig.* 3. The percentage decline in weight is greatest during the first 6 months (22·0 ± 5·9), reaching 32·4 ± 8·3 by the end of the first year. Thereafter the weight loss slows to 35·4 ± 8·6 per cent at 18 months and 36·7 ± 9·4 by 2 years. Mild weight regain of up to 10–12 kg may occur but most patients learn rapidly to control this by modest restraint of their excessive eating.

Mechanism of weight reduction

Whilst there is no doubt that malabsorption, as evinced by steatorrhoea, occurs after jejuno-ileal bypass, there is evidence that reduced appetite and consequent diminished calorie intake explain adequately the loss of weight achieved (Pilkington et al., 1976; Bray et al., 1977). Weight reduction ceases due to restoration of appetite and adaptive changes in the functioning jejuno-ileum which are manifest as dilatation, elongation and mucosal hyperplasia.

Thus, in the creation of jejuno-ileal bypass there is some logic in utilizing maximal lengths of jejunum and ileum, sufficient to achieve adequate weight reduction and to take further advantage of the spontaneous impairment of appetite by further dietary restraint over the succeeding 18–24 months. The potential hazards of nutritional deficiencies would thereby be reduced, especially if a high protein, restricted calorie diet were adopted.

Beneficial effects

Apart from marked and sustained reduction in excess body weight, the main beneficial effects of jejuno-ileal bypass are reduction of hypertensive blood pressure (Fikri and Cassella, 1974) improved respiratory function (Soterakis et al., 1976), psychological rehabilitation, remission of diabetes and reduction of serum lipids.

Psychological and social benefits: Depression, social limitation, marital disharmony, redundancy and unemployment are common complications of massive obesity. Personality disorders may arise as a result of embarrassment, humiliation, lack of self-esteem, fears of rejection and loss of self-confidence. After small bowel bypass mild optimism and euphoria occur in the expectation of future slimness and good health. The patients become more confident and socially active. They are able to acquire work or cope better with domestic or occupational commitments. Pregnancy has occurred normally and without complication after weight reduction has ceased (Baddeley and Fielding, 1977). At the other extreme, severe psychiatric disturbances have been reported (Abram et al., 1976; DeWind and Payne, 1976), though others have found them to be infrequent (Brewer et al., 1974; Solow et al., 1974; Castelnuovo-Tedesco and Schiebel, 1976).

Diabetes: This complication is three to four times more common in the obese than the slim and can be corrected by weight reduction.

Thirteen of the present series of patients were either already known diabetics (4 patients) or found to be so on routine preoperative assessment by fasting blood sugar and glucose tolerance tests. When reassessed 9–44 months after jejuno-ileal bypass all but one had normal blood sugar levels (*Fig.* 4) and even that one patient showed only mildly raised levels. Glucose tolerance had returned to normal in 8 patients, 4 showed miscellaneous abnormalities of much less marked severity and one retained a florid diabetic type of curve (Fielding and Baddeley, 1978). None of the patients required hypoglycaemic therapy.

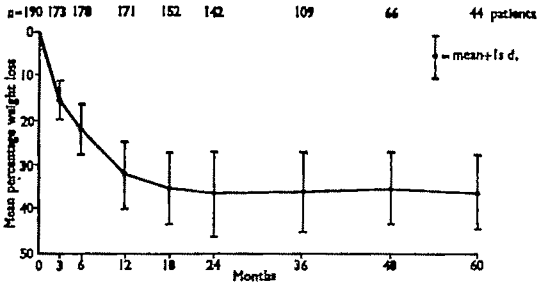


Fig. 3. Mean percentage weight loss after jejuno-ileal bypass.

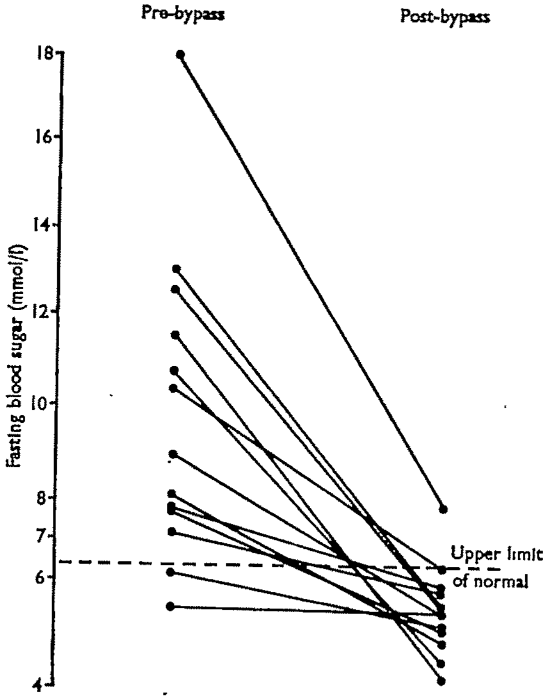


Fig. 4. Changes in blood sugar level before and after jejunal ileal bypass.

Reduction of serum lipids: Jejuno-ileal bypass reduces the amount of mucosal surface available for fatty acid absorption and causes bile acid deficiency by partial interruption of the enterohepatic circulation. As a result of the loss of bile salts in the stool, steatorrhea is further exacerbated. Mobilization of lipids from peripheral stores occurs, allowing a compensatory increase in bile acid synthesis by the liver.

The effects of these changes upon serum cholesterol and triglyceride values are shown in *Fig.* 5. Significant falls were seen during early postoperative months and sustained during the 5-year follow-up period. Reversion of type IV hyperlipidaemia to normal electrophoretic pattern has been a common finding. Similar observations have been made in other series (Scott et al., 1977).

Hazards

Mortality: There have been 2 deaths in 226 patients during the first postoperative month (0·9 per cent). These were due to massive pulmonary embolism and to inhalation of gastric contents, the latter being a case of Praade–Willi syndrome.

Late mortality consisted of 11 deaths, 4 (1·8 per cent) of which were due to myocardial infarction, subacute bacterial endocarditis, acute suppurative pyelonephritis and to accident. In the 7 patients (3·1 per cent) in whom death was attributable to the effects of jejuno-ileal bypass, liver pathology was outstanding. Two patients had cirrhosis (1 alcoholic) and 4 had hepatic failure associated with severe fatty liver. One patient who died from peritonitis following operation to restore bowel continuity because of active urinary tuberculosis, also had a very fatty liver.

This mortality is in keeping with the average incidence of 3·1 per cent (0–11·5 per cent) in 2500 patients culled from the literature by Bray et al. (1977).

Morbidity: The extreme degree of obesity which is prerequisite to the performance of jejuno-ileal bypass purveys an inevitable risk of early surgical complications, such as wound and chest infections, deep vein thrombosis and pulmonary embolism. Liposerous discharge due to fat necrosis in the cut surfaces of the wound is commonly complicated by secondary infection and the likelihood of incisional hernia.

Diarrhoea is inevitable in the early weeks, but the mean stool frequency at 3 months, 4·6 times daily, decreased gradually to 2·8 times daily by 18 months. Excessive diarrhoea of 6 or more stools a day occurred in 25·6 per cent of the patients at 3 months, fell to 12·5 per cent at 6 months and gradually diminished to 6 per cent by 2 years. Such excess was often associated with anal soreness, exacerbation of haemorrhoids or even anal fissure. Most patients overcame the problem by restraint of food and fluid intake together with an antidiarrhoeal.

Fluid and electrolyte deficiencies: During the early months some patients experienced vomiting in addition to diarrhoea and, as a result, developed fluid and electrolyte depletion. Thirty-two patients (16·4 per cent) required admission to hospital for intravenous repletion which was given as a 'cocktail' containing sodium, potassium, magnesium and calcium, administered over 48 h. This was most efficacious in restoring physical and biochemical well-being, but in patients where features of fatty liver were also present parenteral nutrition was instituted until liver function tests returned to normal.

Hypokalaemia: Despite prophylactic oral administration of potassium, 21·8 per cent of patients developed low serum values during the first 6 months, the problem gradually becoming less thereafter as diarrhoea diminished in frequency. Clinical features such as weakness, muscle pain, cramps, nausea and further vomiting were seen in all these cases and were eliminated by repletion. Whole body potassium estimations also revealed low normal values in some patients who were asymptomatic and indicated the need for continued oral repletion for several months.

Hypomagnesaemia was less common in the early months but its incidence gradually increased with time. In many patients the serum values were only marginally low and not associated with symptoms.

Hypocalcaemia occurred in less than 5 per cent of patients in the early months after operation, in contrast to incidences of 20–25 per cent in some reports (Bendezu et al., 1976). Muscle cramps and carpopedal spasm occurred in 4 patients.

Evidence of osteomalacia was sought in routine annual bone biopsies. Of 50 patients followed for 4–5 years, minimal evidence of osteomalacia was found in 5, 1 of whom exhibited symptoms of bone pain and weakness. Demineralization of bone has been reported by Dano and Christiansen (1974) and by Compston et al. (1978), but has not been a feature of other reports.

Abnormal liver function tests were common in the first postoperative year but most, with the exception of alkaline phosphatase, had largely returned to normal by the end of that period (*Fig.* 6).

Acute fatty liver: Only when multiple serum biochemical abnormalities were present were patients liable to exhibit symptoms of anorexia, nausea or vomiting, lethargy and weakness. Liver biopsy showed severe fatty infiltration and, in some patients, cell necrosis.

The acute fatty liver syndrome occurred in 18 patients (*Fig.* 7). Three deaths occurred during treatment by conventional parenteral nutrition regimens and 2 followed operations to restore normal intestinal continuity. These deaths, due to liver failure in 3 and septicaemia in 2, occurred before the report of Heimburger et al. (1975), who showed that parenteral calorie-free amino acid infusion therapy reduced fatty infiltration and repleted the deficiencies of essential amino acids seen by Moxley et al. (1974). Since using the Heimburger regimen, there have been no deaths from this cause.

Altogether 15 patients have responded to parenteral nutrition and 7 have not had further recurrence. Eight patients relapsed and have had normal small bowel continuity restored. Survivors have complete remission of symptoms.

Liver histology: Intraoperative liver biopsies show that 88·4 per cent of the patients had some degree of *fatty infiltration* of the liver parenchyma before jejuno-ileal bypass. The reported incidence has ranged from 65 to 94 per cent (Marubbio et al., 1976).

After jejuno-ileal bypass the severity of fatty change increased in 55·4 per cent of biopsies (*Table II*) but gradually diminished during succeeding years. Even so, by 5 years, 20 per cent of patients still exhibited greater fatty infiltration than that seen on their initial biopsy.

Other postoperative histological abnormalities have included granulomas, portal fibrosis and cirrhosis. Histiocytic granulomas were seen in 16 per cent of 175 patients, being present in the original biopsy of 4 of them. They have varied in frequency from time to time in the same patients, but their significance is not understood.

Early micronodular *cirrhosis* was seen in 4 patients who were biopsied during routine investigations of their obesity or at the time of the intended jejuno-ileal bypass. All of them were, therefore, rejected and the bypass was not performed. Of the 175 patients who have undergone at least one postoperative annual liver biopsy, 15 (8·6 per cent) have subsequently developed early micronodular cirrhosis.

Table II: CHANGES IN HEPATIC FATTY INFILTRATION AFTER JEJUNO-ILEOSTOMY

Year	No. of patients	No change	Improved	Worse
1	132	38	41	73 (55·3)
2	103	25	32	46 (44·7)
3	81	22	28	31 (38·3)
4	44	13	21	10 (22·7)
5	25	9	11	5 (20·0)

Figures in brackets are percentages.

Three deteriorated and have died following discontinuance of the bypass, 2 from liver failure and 1 from hepatorenal syndrome.

The histological features of cirrhosis were recognized at 1 year in 6 patients, at 2 years in 2, at 3 years in 4, in the fifth year in 2 and the sixth year in 1. In only 2 patients could alcoholism have been incriminated as an aetiological factor. Apart from 5 of these cirrhotic patients, each of whom had undergone restoration of small bowel continuity, none has exhibited symptoms or signs of cirrhosis. All have been reluctant to consider reoperation and have been treated by high protein diet and total abstinence from alcohol. Annual biopsies have not revealed further deterioration but should any indication of this occur, it is proposed to discontinue the bypass.

There have been other reports of cirrhosis following jejuno-ileal bypass (Marubbio et al., 1976). Soyer and his colleagues (1976) showed that the cirrhotic change was reversible if small bowel continuity was restored. Disappearance of cirrhotic features was seen in one patient in the present series without reversal of the shunt.

Abdominal bloating: A common complaint after the first year has been abdominal bloating, often associated with embarrassing flatus. Passage of the latter provides some relief but the distension, which usually occurs after large meals, gradually passes off spontaneously over a few hours.

Of 109 patients who replied to a questionnaire, 67·6 per cent complained of this discomfort to a greater or lesser degree. Fifty-six per cent admitted that it was almost always associated with excessive and/or irregular eating habits and that reduction of intake to more normal amounts avoided the problem. Forty per cent found no such benefit, but in these both the distension and the flatus could be controlled with repeated courses of tetracycline or metronidazole. Such treatment unfortunately carries the risk of bacterial resistance and has been used only where all else failed.

The cause of the distension is overgrowth of obligate anaerobes which evoke marked gaseous dilatation of the colon (Barry et al., 1977).

Polyarthralgia and polymyalgia: Multiple small and large joint pains, often simulating rheumatoid arthritis, occurred to a varying extent in 42·4 per cent of 139 patients whose duration of follow-up was 2–6 years. It was severe in 11 per cent and 2 patients required discontinuance of the bypass.

Bouts have usually lasted 1–4 days and have occurred without obvious provocation. The symptoms in some were severely incapacitating and distressing but most frequently the condition is mild and transient. There were no joint changes seen on physical or radiological examination. Serological tests

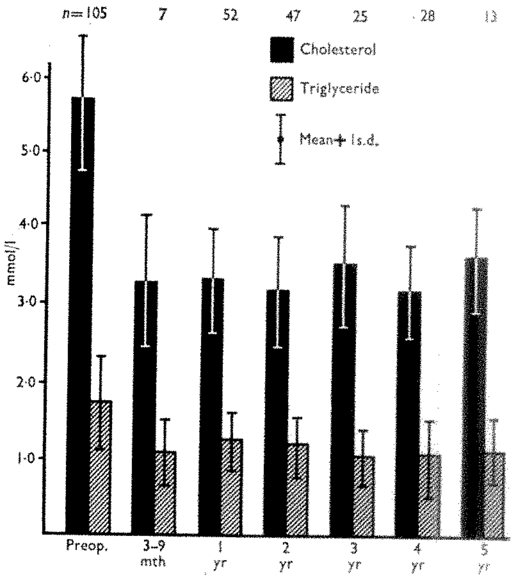


Fig. 5. Changes in fasting serum cholesterol and triglycerides. P value, cholesterol ←<0·001→; triglyceride ←<0·05→<0·01 ←<0·05→.

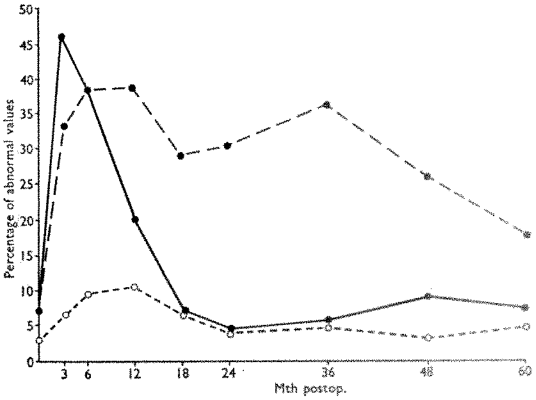
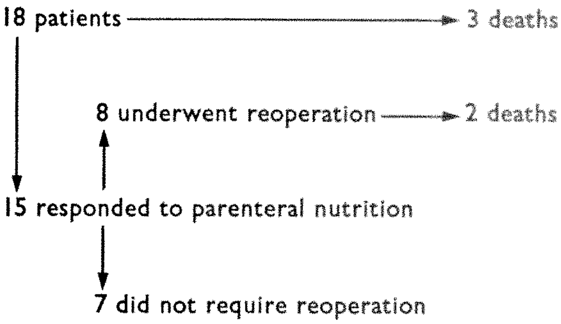


Fig. 6. Incidence of abnormal serum biochemical liver function tests. ●——●, SGOT; ● - - ● alkaline phosphatase; ○ - - ○, albumin.



18 patients
3 deaths
8 underwent reoperation
2 deaths
15 responded to parenteral nutrition
7 did not require reoperation

Fig. 7. Fate of 18 patients suffering from acute fatty liver.

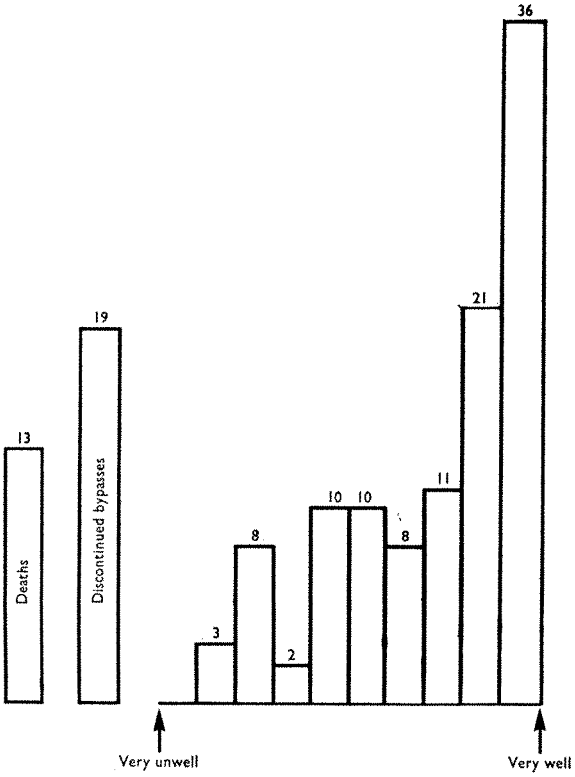


Fig. 8. Subjective state of well-being after jejuno-ileal bypass.

for rheumatoid arthritis, lupus erythematosus cells and antinuclear factor were always negative.

Symptoms usually responded to cotrimoxazole or metronidazole and analgesic after 48–72 h. This indicates an infective cause and evidence in support has been produced by Wands et al. (1976), who showed the presence of circulating cryoprotein immune complexes and complement activation suggestive of systemic absorption of intestinal bacterial antigens, presumably from colonization of the bypassed small bowel.

Other series have reported the occurrence of these side effects in up to 16 per cent of patients (DeWind and Payne, 1976; Wands et al., 1976).

Renal and biliary calculi: Renal calculi of oxalate type have been reported in as many as 30 per cent of patients after jejuno-ileal bypass (Bray et al., 1977). Most surgeons have found the incidence of renal calculi to be 5–10 per cent, and in the present review 5 per cent of 139 patients followed for 2–5 years suffered this side effect. There was, however, no evidence of permanent renal damage in any patient.

Prevention of further renal oxalate calculi by a low oxalate diet has been totally effective in the 7 patients so affected. Alternative treatment would be cholestyramine administration, low fat diet or oral supplements of calcium or taurine.

Although an increased incidence of biliary calculi after jejuno-ileal bypass has been reported (Wise and Stein, 1975; DeWind and Payne, 1976; Merscheimer et al., 1977), it is difficult to substantiate in uncontrolled series of patients who, by the nature of their obesity, are prone to gallstone formation. Studies of bile composition and its lithogenic index (Wise and Stein, 1975; Barry et al., 1977) suggest that biliary calculi would be most likely to occur during the first 6 months after bypass, but thereafter such changes revert to normal.

In the present series there has not appeared to be any excessive incidence of biliary calculi.

Vitamin B12 absorption: Impaired absorption of vitamin B12 has been reported in a number of series (Barry et al., 1977) and is partly due to the short length of ileum available and to bacterial colonization of the small bowel. The pattern of change in serum vitamin B12 levels in the present study has been one of decline to low normal values during the first 18 months, but stabilization thereafter. Only 7 patients in the series developed subnormal values.

Small bowel reconstitution

Because of serious or excessive side effects 19 patients have undergone reoperation to restore normal small bowel continuity. There were 4 deaths, all in patients suffering from liver complications.

The commonest and most serious indication for discontinuance of the bypass was acute fatty liver where incipient liver failure was present (7 patients). Early cirrhosis detected on routine annual liver biopsy has been a further indication for discontinuance of the bypass (3 patients). Other indications have occurred in patients where the discomforts of non-hazardous side effects outweighed the benefits of weight loss. These have included arthralgia (2 patients) and excessive diarrhoea (3 patients). Four patients have undergone discontinuance of the bypass for vomiting, abdominal distension, depression or giddiness. In all cases, small bowel reconstitution has resulted in complete remission.

Subjective benefits of jejuno-ileal bypass

In view of the large number of major and minor side effects encountered, a questionnaire was circulated to 139 patients who had been followed for a minimum period of 2 years. (Nineteen patients who had undergone discontinuance of the bypass and 13 who had died were obviously excluded.) There were 109 replies. Some of the questions and responses were as follows:

Howwell do you feel now as compared with before the operation? 14 worse, 16 no change, 79 better.

Was it worth undergoing the operation? 3 not worth it, 103 worth it, 3 don't know.

To assess the state of well-being, each patient was asked to mark on a straight line with the extremes labelled 'very unwell' and 'very well', where they felt themselves to be. The replies are shown in *Fig.* 8.

It can be seen that the large majority of patients felt subjectively much benefited by jejuno-ileal bypass despite the various side effects which affected some patients to a varying degree.

Conclusions

It is apparent that jejuno-ileal bypass is an effective method of inducing and sustaining weight reduction in the massively obese when all other techniques have failed. Unfortunately, there are a number of associated side effects, some of which are hazardous to life. There is a low operative mortality (0·9 per cent) but a later mortality of 3·1 per cent, which has been mainly due to liver failure. In the main, however, survivors appear to be gratified by the results of the procedure.

It is clear that careful case selection is imperative. Patients who are below average intelligence, alcoholic, suffering from psychiatric illness, cirrhosis, renal failure, symptomatic heart disease or over the age of 50 years should be excluded. On the other hand, those suffering from well-recognized complications of massive obesity such as diabetes, hypertension and osteoarthritis are acceptable if other basic criteria of selection are fulfilled. Good patient discipline and cooperation are essential and there must be a commitment to follow the instructions and advice of the clinician regarding follow-up, diet and discontinuance of the bypass when this is deemed advisable.

In contrast to the iatrogenic malabsorption created by jejuno-ileal bypass, other surgical techniques for reducing massive obesity—dieting enforced by dental splintage and gastric bypass—are effective by physically preventing overeating. Dental splintage depends on satisfactory dentition and proper motivation to sustain the fluid diet regimen over a period of several months. Of 53 patients managed in this manner by the author, 42 were successfully treated with virtually no side effects over a period of 6 months, losing an average 4·12 kg per month (43·7 per cent of mean excess weight). Thus the weight reduction can be as good or better than that achieved by jejuno-ileal bypass. However, it is very doubtful if the long term results will be sustained as these patients are likely to resume their bad eating habits sooner or later after the restraint of dental splintage has been removed.

Gastric bypass has been used increasingly as an alternative to jejuno-ileal bypass during the present decade. In this procedure a high gastric transection is performed to create a fundic pouch of approximately 150 ml capacity, which is drained by a gastrojejunostomy. The stoma of the latter must not be greater than 1·2 cm in diameter. Using this technique Hermreck et al. (1976), Alden (1977) and Griffin et al. (1977) have all shown weight reduction comparable with that achieved by jejuno-ileal bypass. It remains to be seen whether this is sustained over the long term.

Gastric bypass is technically much more difficult than jejuno-ileal bypass and it is to be expected that the operative mortality will be higher, owing mainly to anastomotic leakage. Early problems due to vomiting are more frequent and there are 2–3 per cent incidences of stomal ulcer and dumping. The latter side effects, however, are much less troublesome than those after jejuno-ileal bypass; there do not appear to be any problems from arthralgia, renal colic or abdominal distension and there is much less hazard to the liver.

Thus, jejuno-ileal bypass is the easier procedure with a lower operative mortality. It has a greater morbidity than gastric bypass and requires closer and more detailed follow-up. On balance, the optimum regimen of management for gross refractory obesity may be weight reduction by dental splintage to an 'operable' level of say 30–40 per cent excess weight, followed by gastric bypass. For patients with poor dentition or those likely to be harmed psychiatrically by severe restraint upon eating, jejuno-ileal bypass is an effective alternative now that its side effects are better understood.

References

ABRAM H. S., MEIXEL S. A., WEBB W. W. et al. (1976) Psychological adaptation to jejuno-ileal bypass for morbid obesity. *J. Nerv Ment. Dis.* **162**, 151–157.

ALDEN J. F. (1977) Gastric and jejuno-ileal bypass. *Arch. Surgery* **112**, 799–806.

BADDELEY R. M. (1977) The surgical management of obesity. In: TAYLOR S. (ed). *Recent Advances in Surgery*, 9. Edinburgh, Churchill Livingstone, pp. 113–132.

BADDELEY R. M. and FIELDING J. W. L. (1977) Pregnancy after jejuno-ileal bypass. *Internat. J. Obesity* **1**, 121–126.

BADEN H. (1974) Bypass operations in treatment of obesity. *Ann. Chir. Gyn.* **63**, 365–372.

BARRY R. E., BARISCH J., BRAY G. A. et al. (1977) Intestinal adaptation after jejuno-ileal bypass in man. *Am. J. Clin. Nutr.* **30**, 32–41.

BENDEZU F., WEILAND R. G., GREEN S. G. et al. (1976) Certain metabolic consequences of jejuno-ileal bypass. *Am. J. Clin. Nutr.* **29**, 366–370.

BRAY G. A., GREENWAY F. L., BARRY R. E. et al. (1977) Surgical treatment of obesity: a review of our experience and an analysis of published reports. *Intern. J. Obesity* **1**, 331–368.

BREWER C., WHITE H. and BADDELEY R. M. (1974) Beneficial effects of jejuno-ileostomy on compulsive eating and associated psychiatric symptoms. *Br. Med. J.* **4**, 314–315.

CASTELNUOVO-TEDESCO P. and SCHIEBEL D. (1976) Studies of super-obesity. 2. Psychiatric appraisal of jejuno-ileal bypass surgery. *Am. J. Psychiatr.* **133**, 26–31.

COMPSTON J., HORTON L. W. L., LAKER M. F. et al. (1978) Bone disease after jejuno-ileal bypass. *Lancet* **2**, 1–3.

DANO P. and CHRISTIANSEN C. (1974) Calcium absorption and bone-mineral contents following intestinal shunt for obesity. *Scand. J. Gastroenterol.* **9**, 775–779.

DEWIND L. T. and PAYNE J. H. (1976) Intestinal bypass surgery for morbid obesity. *JAMA* **236**, 2298–2301.

FIELDING J. W. L. and BADDELEY R. M. (1978) The effect of small bowel bypass on diabetes mellitus. *Br. J. Surg.* **65**, 30–32.

FIKRI E. and CASSELLA R. R. (1974) Obesity: jejuno-ileal bypass for massive obesity—results and complications in 52 patients. *Ann. Surg.* **179**, 460–464.,

GASPAR M. R., MOVIAS M. J., ROSENTAL J. J. et al. (1976) Comparison of Payne and Scott operations for morbid obesity *Ann. Surg.* **184**, 507–515.

GRIFFIN W. O., YOUNG V. L. and STEVENSON C. C. (1977) A prospective comparison of gastric and jejuno-ileal bypass procedures for morbid obesity. *Ann. Surg.* **186**, 500–509.

HEIMBURGER S. L., STEIGER E., GERFO P. L. et al. (1975) Reversal of severe fatty infiltration after intestinal bypass for morbid obesity by calorie free amino acid infusion. *Am. J. Surg.* **129**, 229–235.

HERMRECK A. S., JEWELL W. R. and HARDIN C. R. (1976) Gastric bypass for morbid obesity. *Surg. Gynecol. Obstet.* **80**, 498–505.

KREMEN A. J., LINNER J. H. and NELSON C. H. (1954) Experimental evaluation of nutritional importance of proximal and distal small intestine. *Ann. Surg.* **140**, 439–448.

MARUBBIO A. T., BUCHWALD H., SCHWARTZ M. Z. et al. (1976) Hepatic lesions of central pericellular fibrosis in morbid obesity, and after jejuno-ileal bypass. *Am. J. Clin. Pathol.* **66**, 684–691.

MERSCHEIMER W. L., KAZARIAN K. K. and DURSI J. F. (1977) A critical analysis of 51 patients with jejuno-ileal bypass. *Surg. Gynecol. Obstet.* **145**, 847–852.

MOXLEY R. T., POLEFSKY T. and LOCKWOOD D. H. (1974) Protein nutrition and liver disease after jejuno-ileal bypass for morbid obesity. *N. Engl. J. Med.* **290**, 921–926.

PASSARO E., DRENICK E. and WILSON S. E. (1976) Bypass enteritis. New complication of jejuno-ileal bypass for obesity. *Am. J. Surg.* **131**, 169–174.

PAYNE J. H. and DEWIND L. T. (1969) Surgical treatment of obesity. *Am. J. Surg.* **118**, 141–147.

PILKINGTON T. R. E., GAZET J.-C. ANG L. et al. (1976) Explanations for weight loss after ileo-jejunal bypass in gross obesity. *Br. Med. J.* **1**, 1504–1505.

QUAADE F. (1977) Studies of non-operated obese patients: an interim report on the Scandinavian obesity project. *Am. J. Clin. Nutr.* **30**, 16–20.

SCOTT H. W., DEAN R., SHULL H. J. et al. (1973) New considerations in use of jejuno-ileal bypass in patients with morbid obesity. *Ann. Surg.* **177**, 723–735.

SCOTT H. W., DEAN R. H., SHULL H. J. et al. (1977) Results of jejuno-ileal bypass in two hundred patients with morbid obesity. *Surg. Gynecol. Obstet.* **145**, 661–673.

SOLOW C., SILBERFARB P. and SWIFT K. (1974) Psychological effects of intestinal bypass surgery for severe obesity. *N. Engl. J. Med.* **290**, 300–305.

SOTERAKIS J., GLENNON J. A., SIHIHARA A. M. et al. (1976) Pulmonary function studies before and after jejuno-ileal bypass surgery. *Am. J. Dig. Dis.* **21**, 553–556.

SOYER M. T., CEBALLOS R. and ALDRETE J. S. (1976) Reversibility of severe hepatic damage caused by jejuno-ileal bypass after re-establishment of normal intestinal continuity. *Surgery* **79**, 601–604.

WANDS J. R., LAMONT J. T., MANN E. et al. (1976) Arthritis associated with intestinal bypass procedure for morbid obesity. *N. Engl. J. Med.* **294**, 121–124.

WISE L. and STEIN T. (1975) Biliary and urinary calculi—pathogenesis following small bowel bypass for obesity. *Arch. Surg.* **110**, 1043–1047.

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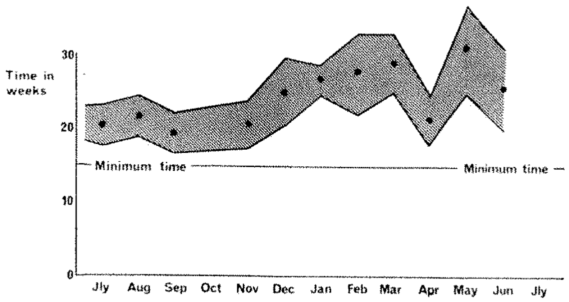

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Muscle and serum adenosine triphosphatase in patients suffering from tetanus

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SUMMARY

Serial estimation of muscle and serum adenosine triphosphatase (ATPase) activity was performed in 16 healthy control patients and 32 cases with tetanus. There was no significant difference due to age and sex in muscle and serum ATPase activity between the normal and tetanus cases. Tetanus patients showed a marked increase in muscle and serum ATPase activity as compared to normal. The ATPase activity increased with the severity of convulsion and disease. There was increased mortality in tetanus patients having higher values of muscle and serum ATPase.

THE severe muscular contractions of tetanus cause physiological disturbances in the body. Changes in acetylcholine and catecholamine levels were shown in experimental tetanus (Mikhailov, 1969, 1971). Muscle acetylcholinesterase has been reported to be lowered in experimental tetanus (Harvey, 1939; Diamond and Mellanby, 1970). The role of adenosine triphosphatase (ATPase) in muscle contraction is well known (Engelhardt and Ljubimowa, 1939; Szent, 1947). Activation of muscle and brain ATPase in mice by tetanus intoxication was reported by Asakura et al. (Asakura et al., 1951; Asakura et al., 1958a, b). There is no published similar study in human beings. It was, therefore, considered of interest to study muscle and serum ATPase in tetanus patients and the results are described below.

Patients and methods

A total of 16 healthy controls (10 males and 6 females varying in age from 10 years to 40 years) and 32 cases of tetanus (20 males and 12 females varying in age from 5 years to 50 years) admitted to King George's Medical College and Hospital, Lucknow, have been studied. Cases of tetanus in the newborn and in infants have been excluded from the study. The severity of tetanus has been graded according to the classification of Patel and Joag (1959).

The blood sample and muscle from the gastrocnemius were taken at the time of doing venous cutdown before administering any treatment. Estimations of serum and muscle ATPase activity were performed using the method of Kielley and Kielley (1951). Inorganic phosphate was estimated in the protein-free filtrate by the method of Fiske and Subbarow (1925) and protein estimated by the method of Lowry et al. (1951).

Results

No significant difference was observed in muscle and serum ATPase activity in normal control and tetanus cases with regard to age and sex (*Tables I* and *II*). ATPase activity of muscle and serum was found to be increased in tetanus patients when compared with controls ($P<0·01$, by Student's *t*-test after analysis of variance) (*Tables I* and *II*). The increase in muscle ATPase activity was 55·4 per cent and in serum ATPase activity 44·7 per cent, respectively (*Fig.* 1). With increasing severity of convulsions there was a significant increase in muscle and serum ATPase activity in tetanus patients (*Table III*). The severity of tetanus is directly related to the muscle and serum ATPase activity ($P<0·01$) (*Fig.* 2, *Tables I* and *II*). Values of muscle and serum ATPase activity were higher in those who died than in those who survived (*Table IV*).

Discussion

Asakura et al. (1958a, b) have studied the mode of action of tetanus toxin, ATPase activation by tetanus intoxication and specificity of the ATPase. They found ATPase activation in muscle and brain of tetanus-toxin-intoxicated mice. In the present study it has

Table I: MUSCLE ATPase ACTIVITY IN CONTROL AND TETANUS PATIENTS

Age:	≤30 yr	>30 yr	All ages
C	75·0±1 4 (8)	73·2±3·3 (8)	74·1±1·8 (16)
T_1	98·1±1·8 (7)	100·4±2·1 (5)	99 1±1·8 (12)
T_2	118·3±1·7 (7)	120 4±2 1 (7)	119·4±1 3 (14)
T_3	136·0±2 2 (4)	134·0±2·0 (2)	135 3±1·5 (6)
Sex	Male	Female	
C	72·3±2·2 (10)	77·2±2·8 (6)	
T_1	99·3±2·4 (6)	99·8±2·8 (6)	
T_2	122·0±1·2 (8)	115·8±1·9 (6)	
T_3	135·3±1·5 (6)	—	
Age: Sex	≤30 yr	>30 yr	All ages
C Male	73 6±1·7 (5)	71 0±4·2 (5)	72 3±2·2 (10)
C Female	77·3±2·3 (3)	77·0±5·7 (3)	77 2±2·8 (6)
T_2 Male	119·8±1·9 (4)	124·2±0 25 (4)	122·0±1·2 (8)
T_2 Female	116·3±3 0 (3)	115·3±2·9 (3)	115·8±1·9 (6)

Values for ATPase are expressed as mean±s.e. mean μmol inorganic phosphate/g protein/20 mt. Figures in parentheses denote numbers of cases.

C, Control; T_1, mild tetanus; T_2, moderate tetanus: T_3, severe tetanus.

Table II: SERUM ATPase ACTIVITY IN CONTROL AND TETANUS PATIENTS

Age:	≤30 yr	>30 yr	All ages
C	38·6±1·5 (8)	38·6±1·3 (8)	38·6±0·98 (16)
T_1	47 7±0·56 (7)	49·4±1·5 (5)	48·4±0·71 (12)
T_2	54 7±0·71 (7)	59·6±0·61 (7)	57·1±0 81 (14)
T_3	67 2±1·8 (4)	65·5±0·50 (2)	66·7±1·2 (6)
Sex:	Male	Female	
C	38·5±1·2 (10)	38·8±1·5 (6)	
T_1	48·7±1·0 (6)	48·2±1·1 (6)	
T_2	57·5±1·2 (8)	56·7±1·1 (6)	
T_3	66·7±1·2 (6)	—	
Age: Sex	≤30 yr	>30 yr	All ages
C Male	38·0±2·2 (5)	39·0±1·1 (5)	37.5±1·2 (10)
C Female	39·7±2·3 (3)	38·0±2·3 (3)	38·8±1·5 (6)
T_2 Male	54·8±1·2 (4)	60 2±0 25 (4)	57 5±1·2 (8)
T_2 Female	54·7±0·66 (3)	58·7±1·3 (3)	56·7±1·1 (9)

Values for ATPase are expressed as mean±s.e. mean μmol inorganic phosphate/g protein/20 mt. Figures in parentheses denote numbers of cases.

C, Control; T_1, mild tetanus; T_2, moderate tetanus; T_2, severe tetanus.

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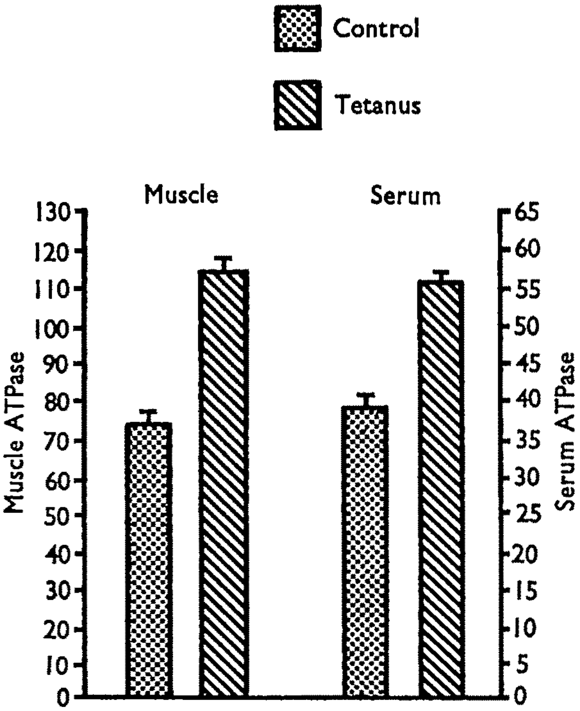

Fig. 1. ATPase (μmol inorganic phosphate/g protein/20) in control and tetanus patients.

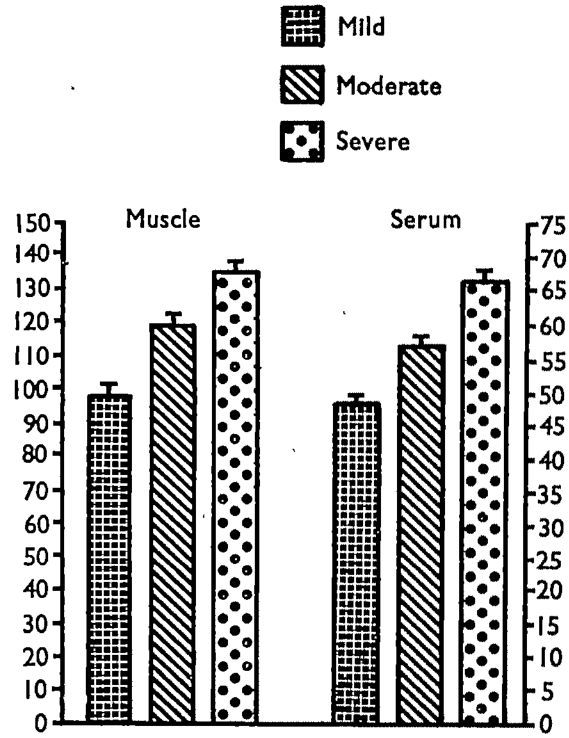

Fig. 2. ATPase (μmol inorganic phosphate/g protein/20) related to severity of disease.

Table III: SEVERITY OF CONVULSIONS AND ATPase ACTIVITY

Degree of convulsions	No. of cases	ATPase activity Muscle	Serum
Grade I (mild)	10	99·80±1·8	49·50±0·8
Grade II (moderate)	13	114·44±1·5	54·46±0·9
Grade III (severe)	9	131·80±2·1	64·22±1·1

Values are expressed in mean±s.e. mean as μmol inorganic phosphate/g protein/20 mt.

Table IV: ATPase ACTIVITY AND END RESULT

End result	No. of cases	ATPase activity Muscle	Serum
Survived	14	109·71±1·7	53·36±0·98
Died	16	120·50±1·9	58·00±1·10

Values are expressed as mean±s.e. mean μmol inorganic phosphate/g protein/20 mt.

been clearly demonstrated that there is a marked increase in muscle and serum ATPase activity in tetanus patients as compared with normal controls. Neither muscle nor serum ATPase activity were affected significantly by age or sex, both in controls and in tetanus patients. Asakura et al. (1958a, b) have shown that in experimental tetanus the rate of activation of enzyme closely parallels the severity of symptoms regardless of whether the condition is proceeding or in remission. The present study shows a significant increase in muscle and serum ATPase activity with increasing severity of convulsions and disease.

References

ASAKURA S., SEKI T. and IGA I. (1951) Tetanal intoxication and metabolism of central nervous tissue. *Med. J. Osaka Univ.* **2,** 35–42.

ASAKURA S., SEKI T., KAMBAYASHI T. et al. (1958a) Mode of action of tetanal toxin. ATPase activation by tetanal intoxication and specificity of ATPase. *Med. J. Osaka Univ.* **8,** 653–661.

ASAKURA S., SEKI T., OKI S. et al. (1958b) Mode of action of tetanal toxin. *In vitro* action of tetanal toxin upon adenosine triphosphatase activity. *Med. J. Osaka Univ.* **8,** 279–288.

DIAMOND J. and MELLANBY J. (1970) Effect of tetanus toxin in the goldfish. *J. Physiol.* **210,** 186.

ENGELHARDT W. A. and LJUBIMOWA M. N. (1939) Myosine and adenosine triphosphatase. *Nature* (*Lond.*) **144,** 668–669.

FISKE C. H. and SUBBAROW I. (1925) The colorimetric determination of phosphorus. *J. Biol. Chem.* **66,** 375.

HARVEY A. M. (1939) Effect of tetanus toxin on skeletal muscle. *J. Physiol.* **95,** 30.

KIELLEY W. W. and KIELLEY R. K. (1951) Myokinase and adenosine triphosphatase in oxidative phosphorylation. *J. Biochem.* **191,** 485.

LOWRY O. H., ROSEBROUGH N. J., FARR A. L. et al. (1951) Protein measurement with the Folin phenol reagent. *J. Biol. Chem.* **193,** 265–275.

MIKHAILOV V. V. and CHEKHOVSKAIA L. A. (1969) Participation of acetylcholine in mechanism of axoplasmic transport disruption in thick myelinated nerve fibres in experimental tetanus. *Biull. Eksp. Biol. Med.* **67,** 48–51.

MIKHAILOV V. V. and CHESNOKOVA N. P. (1971) Changes in catecholamine content of tissue in experimental tetanus. *Biull. Eksp. Biol. Med.* **71,** 20–24.

PATEL J. C. and JOAG G. G. (1959) Grading of tetanus to evaluate prognosis. *Ind. J. Med. Soc.* **13,** 831–833.

SZENT G. A. (1947) *Chemistry of Muscle Contraction.* New York, Academic Press.

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Influence of thyroid surgery on voice function and laryngeal symptoms

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SUMMARY

A comprehensive examination of voice function and laryngeal symptoms was applied systematically to 20 patients undergoing thyroid surgery. Patients were excluded from the series if there had been previous neck surgery, or if postoperative indirect laryngoscopy showed abnormal cord mobility. Examination before operation showed that patients with sporadic non-toxic goitre or medically pre-treated toxic goitre had impaired voice function based on stroboscopy, electroglottography, phono-oscillometry and determination of voice range, phonation time, pitch, and peak flow. Three months after thyroid surgery the voice function was significantly improved although not normal in non-toxic goitre patients, whereas the voice function in patients with thyrotoxicosis was unchanged. The number of laryngeal symptoms was significantly reduced in non-toxic goitres following surgery and unaltered in the group with thyrotoxicosis.

THYROID surgery and laryngeal function are intimately associated because of the anatomical relations between the gland, larynx and supplying nerves. Laryngoscopy is recommended to evaluate vocal cord mobility after thyroid surgery (Leading Article, 1977), but is insufficient to detect minor, but none the less important, changes in the vocal function of the larynx. More refined methods are required (Watt-Boolsen et al., 1977). When advocating surgical treatment of thyroid diseases, the possible influence on voice function is of great concern. Remarkably, detailed knowledge of this subject is lacking.

In our study, a comprehensive examination of voice function and laryngeal symptoms has been carried out systematically in patients undergoing thyroid surgery.

Patients and methods

Twenty patients, of whom 16 were female and 4 male, aged between 18 and 72 years with a median of 34 years, underwent thyroid surgery. Twelve patients had a sporadic non-toxic goitre and 8 had a medically pre-treated toxic goitre. At the time of operation all patients were euthyroid clinically and biochemically as judged by serum thyroxine, serum tri-iodothyronine, serum TSH and T_3-resin uptake tests. None gave a history of voice trouble preceding the development of their thyroid disease. The only criterion for exclusion was previous neck surgery and the development after operation of abnormal vocal cord mobility as judged by indirect laryngoscopy.

Operative procedure

A transverse collar incision was made approximately 3 cm above the suprasternal notch and mid-portion of the clavicle on each side. Upper and lower skin flaps were developed by sharp dissection in a plane of cleavage between the platysma and the fascia covering the strap muscles. The strap muscles were separated in the midline and retracted laterally thereby exposing the thyroid gland. The middle thyroid vein and the vessels at the superior pole were divided and ligated on the side to be resected, whereas the inferior thyroid artery was spared. The recurrent laryngeal nerve was not deliberately identified in any instance. A suction drain was brought out through the lateral angle of the wound. All operations had an uneventful course and no wound complications occurred. Indirect laryngoscopy was normal preoperatively as well as on the fifth postoperative day in all cases. The patients with thyrotoxicosis had a sub-total resection of each lobe. Of the patients with sporadic goitre, 3 had a bilateral resection of a multinodular goitre and 9 a unilateral resection of a single nodule. The weight of the removed tissue varied between 6 and 175 g, with a median of 29 g. The weight of removed tissue did not differ significantly between the two groups.

Table I: SCORE SYSTEM FOR EVALUATION OF VOICE FUNCTION

Parameters	Results	Score
Stroboscopy	Regular	1
	Irregular	0
Electroglottography	Regular	1
	Irregular	0
Phono-oscillometry	Regular	1
	Irregular	0
Voice range (semitones)	≥24	3
	24–19	2
	18–13	1
	≤12	0
Phonation time (s)	≥20	3
	19–15	2
	<15	1
Pitch (semitones)	≥7	2
	6–5	1
	<5	0
Peak flow (% of normal peak flow)	≥75	1
	<75	0
Maximum score		12

All patients remained euthyroid during the period of study. Hypoparathyroidism did not occur a sjudged by serum calcium determinations.

Vocal procedures

The voice function was studied the day before operation and 3 months postoperatively. The examination consisted of stroboscopy, electroglottography, phono-oscillometry and determination of voice range, phonation time, pitch and peak flow. A description of the parameters has been given in a previous study (Watt-Boolsen et al., 1977). Furthermore, the following laryngeal symptoms were registered: a frequent urge to clear the throat and/or to cough, excessive dryness of the throat, an easily fatigued voice, a feeling of a lump and/or tension in the throat and, finally, a feeling of respiratory strain.

The objective data were transferred to a score system described elsewhere (Watt-Boolsen et al., 1977) and given in *Table I.* The normal values of voice range, phonation time, pitch and peak flow are the minimal values found in 700 normal persons examined in our laboratory.

Statistical procedures

The Wilcoxon test was used for paired data and the Mann–Whitney U test for unpaired data. Exact confidence limits were used when comparing patient groups with the normal group. $P<0\cdot05$ was considered significant.

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Table II: ACHIEVED SCORES IN 20 PATIENTS BEFORE AND AFTER THYROID SURGERY

Patients	Preoperative	Postoperative
Non-toxic 1	9	12 (+3)
2	2	4 (+2)
3	10	10 (0)
4	7	8 (+1)
5	10	11 (+1)
6	10	8 (÷2)
7	6	9 (+3)
8	9	9 (0)
9	7	10 (+3)
10	10	11 (+1)
11	8	10 (+2)
12	8	9 (+1)
Toxic 13	8	8 (0)
14	7	5 (÷2)
15	7	9 (+2)
16	5	8 (+3)
17	1	7 (+6)
18	11	8 (÷3)
19	6	5 (−1)
20	4	9 (+5)

Figures in brackets indicate the change in score following surgery.

Table III: NUMBER OF LARYNGEAL SYMPTOMS IN 20 PATIENTS BEFORE AND AFTER THYROID SURGERY

Patients	Preoperative	Postoperative
Non-toxic 1	2	0 (÷2)
2	2	1 (÷1)
3	3	0 (÷3)
4	6	0 (÷6)
5	3	2 (÷1)
6	3	2 (÷1)
7	0	0 (0)
8	4	2 (−2)
9	0	0 (0)
10	0	0 (0)
11	0	0 (0)
12	5	1 (−4)
Toxic 13	1	0 (÷1)
14	2	2 (0)
15	3	3 (0)
16	2	0 (÷2)
17	0	0 (0)
18	3	2 (÷1)
19	0	1 (+1)
20	3	3 (0)

Figures in brackets indicate the change in the number of laryngeal symptoms following surgery.

Results

Prior to operation a comparison between our two groups of patients and the normal group showed that both the non-toxic goitre patients and the patients with pre-treated thyrotoxicosis had a significantly impaired voice function based on the score system. A comparison between the two groups themselves showed no significant difference in voice function or in the number of laryngeal symptoms.

The scores obtained before operation and 3 months after operation are presented in *Table II* and the number of laryngeal symptoms in *Table III*. Indirect laryngoscopy was normal in all cases both before and after operation.

After surgery it was found that the voice function of the non-toxic goitre patients was significantly improved, although still significantly different from normal. The number of scores was increased in 9 patients, unchanged in 2 and decreased in 1 patient. Furthermore, a significant reduction in the number of laryngeal symptoms was noted. On the other hand, in the group with thyrotoxicosis neither the voice function nor the number of laryngeal symptoms was significantly altered after operation.

Discussion

The causes of impaired voice function in patients with benign goitres are not well established. Restricted mobility of the larynx and compression of supplying nerves may be causative factors (De Gandt, 1970). In fact, this assumption is supported by our findings of improved voice function and reduced laryngeal symptoms in the non-toxic group. On the other hand, in our patients with thyrotoxicosis the voice function and laryngeal symptoms were unaltered by surgery, indicating that factors other than purely mechanical ones are involved. The existence of specific disturbances of voice in untreated thyrotoxic patients has been postulated, but not established with certainty (Luchsinger and Arnold, 1949; Kittel, 1969); it was not made clear whether or not treatment with antithyroid drugs improved the phenomenon. The failure to improve voice function and the persistence of laryngeal symptoms in our patients with thyrotoxicosis should be evaluated in the light of this work.

We conclude that surgical management of benign thyroid diseases can be advocated without the fear of causing voice problems provided that a skilful and delicate technique is observed.

References

DE GANDT J. B. (1970) Les compressions récurrentielles. *Acta Otorhinolaryngol Belg.* **4**, 520–554.

KITTEL G. (1969) Die Kehlkopfdystonie bei verstarkter Schilddrusenaktivität. *Folia Phoniatr. (Basel)* **21**, 39–46.

LEADING ARTICLE (1977) Damaged laryngeal nerves in thyroid surgery. *Br. Med. J.* **2**, 416–417.

LUCHSINGER R. and ARNOLD G. E. (1949) *Lehrbuch der Stimm- und Sprachheilkunde.* Vienna, Springer-Verlag, pp. 112–114.

WATT-BOOLSEN S., BLICHERT-TOFT M., HANSEN J. B. et al. (1977). Late voice function after surgical injury to the recurrent nerve. *Clin. Otol.* **2**, 191–197.

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Lingual thyroid: a review of 12 cases

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SUMMARY

Twelve patients with lingual thyroid are reviewed. Two of these patients had a follicular carcinoma in the ectopic gland and both are well 5 and 16 years after treatment.

The diagnosis is essentially clinical but confirmation may be made with a thyroid scan.

Six patients were treated conservatively with thyroxine with good results. Six patients were treated by surgical excision, 2 undergoing autotransplantation of the excised gland into the anterior abdominal wall.

LINGUAL ectopia of the thyroid gland is a rare congenital anomaly caused by failure of the thyroid duct to migrate from the foramen caecum to the usual pre-laryngeal site. Hickman (1869) was the first to describe the condition when reporting the case of a female neonate who died of suffocation from a lingual thyroid 16 h after birth. Since then sporadic case reports have appeared in the literature with an extensive review by Montgomery in 1936. Although Krishnamurthy and Blahd (1972) recorded that 373 cases of lingual thyroid had been reported in the world literature, there has been no recent series published in the British literature.

Carcinoma developing in a lingual thyroid is exceedingly rare and Fish and Moore (1963), in an exhaustive review, could find only 21 published cases. Recently, we encountered two cases of lingual thyroid, one of which was found to be malignant, and this led us to review our hospital records.

Patients and methods

The case records of patients attending the Tata Memorial Hospital, Bombay, between January 1961 and December 1974 were reviewed. Twelve patients with a lingual thyroid had been seen in addition to 4045 patients with thyroid enlargement.

Nine of the patients were female. The age of distribution is shown in *Fig.* 1, the majority of the patients presenting in the second or fourth decades of life.

Symptoms

All the patients complained of dysphagia and an awareness of a foreign body in the throat. Six complained of a change in the quality of their speech. A cough when lying down was the other common symptom. Bleeding from the gland was the main problem in 1 patient. In 3 patients the symptoms appeared to have been precipitated by pregnancy. Duration of the symptoms ranged from 1 week to 6 months although 2 patients had been aware of an asymptomatic swelling for many years.

Diagnosis

The diagnosis was mainly clinical and was made by the characteristic appearance of a swelling in the region of the foramen caecum (*Fig.* 2). The swelling was fleshy, sessile and sometimes ulcerated.

In 8 patients the diagnosis was confirmed by radioactive iodine scan which showed concentration of the isotope at the base of the tongue and absence of isotope in the neck (*Fig.* 3). In one patient additional thyroid tissue was shown at the level of the hyoid.

Treatment

Six patients were treated conservatively with thyroxine. One of these patients has been lost to follow-up. The other 6 patients were treated operatively because of the severity of symptoms associated with recent enlargement and the inability to exclude malignant change.

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Technique of operation

A preliminary temporary tracheostomy was performed so as to avoid possible obstruction of the airway from oedema of the base of the tongue and larynx in the postoperative period. The lingual arteries were ligated on either side of the neck through separate skin incisions at the level of the cornu of the hyoid bone. After inserting stay sutures on either side, the tongue was then cut along the midline fibrous septum (*Fig.* 4). Bleeding was minimal if the incision was kept strictly in the midline.

The tongue was then pulled forward and the lingual thyroid excised. The thyroid tissue is partly in the substance of the tongue and excision in depth is necessary. The tongue was then sutured with chromic catgut and a piece of the gland sent for frozen section histological examination. If there was no evidence of malignancy the excised thyroid tissue was sliced into thin sections and implanted within the anterior rectus sheath.

Results

In 5 of the 6 patients who had conservative treatment the symptoms were controlled, the follow-up ranging from 3 to 10 years. One patient was lost to follow-up, however, and the outcome is unknown.

Of the 6 patients who underwent operation, 2 were found to have a follicular carcinoma of the lingual thyroid. One of these patients, a boy of 12 years, has already been reported (Potdar and Desai, 1971) and he remains well 16 years after treatment with thyroid replacement therapy.

The second patient with a follicular carcinoma was a 40-year-old woman who was shown to have residual thyroid tissue at the base of the tongue by an ^{123}I scan performed after the operation. This was ablated with radioactive iodine and the patient is well 5 years later with thyroid replacement therapy.

The remaining 4 patients had a benign lingual thyroid. Implantation of the excised thyroid tissue into the anterior rectus sheath was performed in 2 patients. The third patient did not need implantation because of the presence of normal thyroid tissue in the neck. Implantation was not performed in the fourth patient for unknown reasons. Two of these 4 patients, 1 who had thyroid implantation and 1 who did not, developed myxoedema and required supplementary hormone therapy. The cause of failure of autotransplantation in 1 patient is not known.

Discussion

Although rare, lingual thyroid may be more common than suggested by the literature, as generally only symptomatic patients will present to the doctor. Of all reported patients 70–80 per cent are female. Our series confirms this sex difference, the cause of which is uncertain. It may possibly be associated with a higher physiological demand in women during puberty and pregnancy, causing hypertrophy. The two peaks

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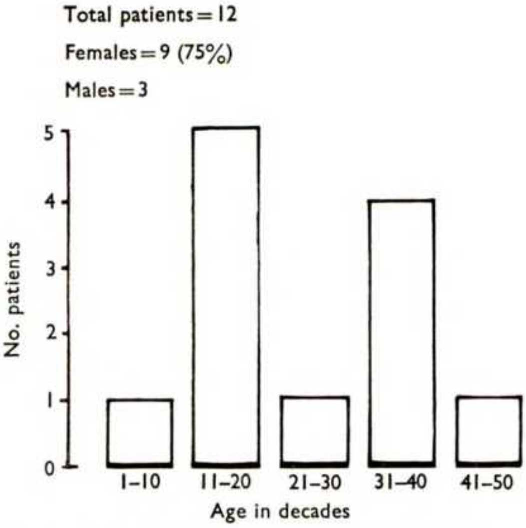

Fig. 1. The age distribution in 12 patients with lingual thyroid.

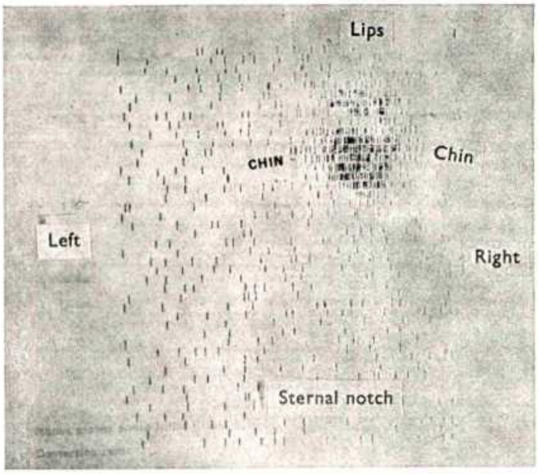

Fig. 3. ^{131}I scan of a patient with a lingual thyroid. Note the concentration of ^{131}I at the base of the tongue and the complete absence of radioactivity in the neck.

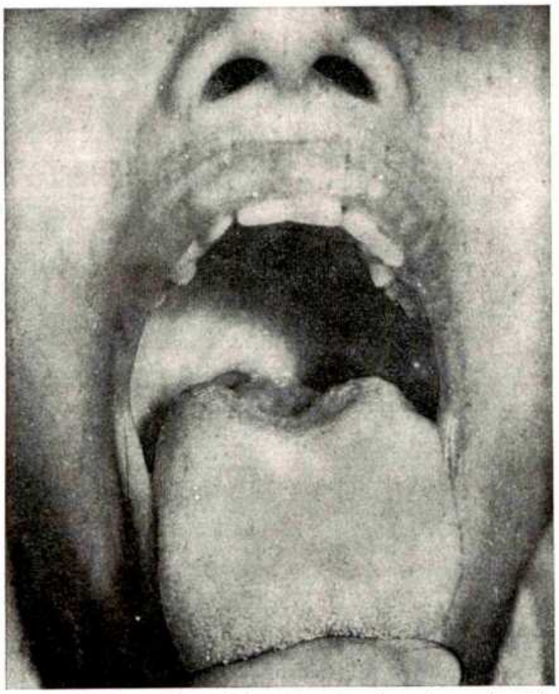

Fig. 2. Showing a lingual thyroid arising from the region of the foramen caecum.

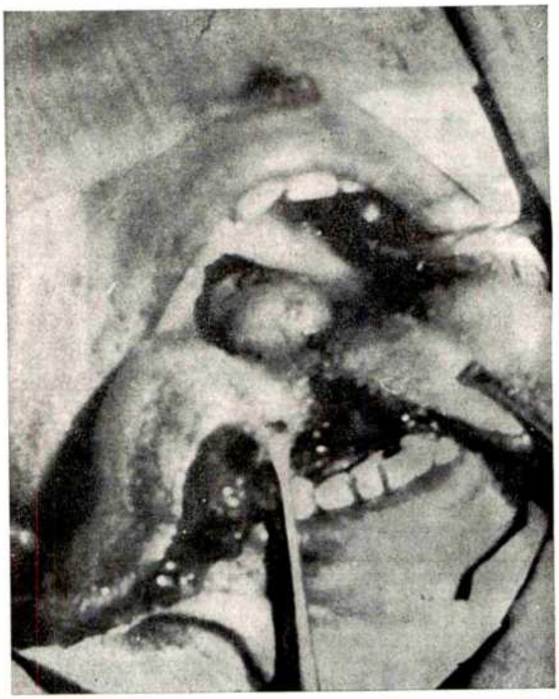

Fig. 4. Operative photograph showing midline splitting of the tongue giving excellent exposure of the lingual thyroid.

in the age incidence in our series would support this suggestion.

Treatment of a lingual thyroid depends on the severity of symptoms, the age of the patient, any precipitating factors such as puberty or pregnancy and any complicating factors such as ulceration or haemorrhage. There is also a possibility of malignant change, of which there are no characteristic features. This complication, however, is no more likely than in a normally located thyroid.

Lingual thyroids which are small and asymptomatic can safely be kept under observation without any active treatment, as in 70 per cent of cases the lingual thyroid is the only functioning thyroid tissue (Fish and Moore, 1963). Patients with mild symptoms can be treated with thyroxine until the symptoms disappear. Reduction in the size of the gland is quite slow with thyroxine treatment and no dramatic result should be expected. Six patients in this series who had milder symptoms were treated with thyroid hormone with satisfactory results, although the follow-up period is not long. This has been reported by O'Dell et al. (1959). Patients with severe obstructive symptoms, suspected malignant change, ulceration and haemorrhage or who do not respond to hormonal treatment should undergo surgery.

In our patients we have used an intraoral approach to the ectopic thyroid which we think is simpler than the lateral pharyngotomy approach advocated by Hillness and Black (1976). Autotransplantation of the excised gland into the rectus muscle has been advocated by Swan et al. (1952), Lawson (1957) and Jones (1961). Braunwald and Hufnagel (1958) have shown that the site of transplantation of the thyroid is not of primary importance in tissue survival and the rectus muscle is selected because of the easy access.

In the immediate postoperative period the autotransplanted thyroid tissue may not function well and the patient may have temporary hypothyroidism. These patients should not receive thyroxine, however, or there will be suppression of endogenous secretion of thyroid hormone. Ablation of lingual thyroid tissue with radioactive iodine has been recommended by Schilling et al. (1950) but no immediate relief of symptoms is possible with this method and most of these patients develop late myxoedema. It should be stressed, however, that all patients with lingual thyroid, whether treated conservatively or by surgery, need continued close assessment of their thyroid function.

Two patients of the 12 (16 per cent) had a malignancy in our series, an incidence which is greater than that previously reported. These cases incline us towards surgical excision whenever there is any recent or sudden enlargement of the gland.

References

BRAUNWALD N. S. and HUFNAGEL C. A. (1958) The effect of the site of transplantation and presence of glandular deficiency on the success of thyroid autografts. *Surgery* **43**, 428–434.

FISH J. and MOORE R. M. (1963) Ectopic thyroid tissue and ectopic thyroid carcinoma: a review of the literature and report of a case. *Ann. Surg.* **157**, 212–218.

HICKMAN W. (1869) Congenital tumour of the base of the tongue, pressing down the epiglottis on the larynx and causing the death by suffocation sixteen hours after birth. *Trans. Pathol. Soc. Lond.* **20**, 160–161.

HILLNESS A. D. and BLACK J. E. (1976) Lingual ectopia of the thyroid gland and autotransplantation. *Br. J. Surg.* **63**, 924–926.

JONES P. (1961) Autotransplantation in lingual ectopia of the thyroid gland. Review of the literature and report on a successful case. *Arch. Dis. Child.* **36**, 164–170.

KRISHNAMURTHY G. T. and BLAHD W. (1972) Lingual thyroid associated with Zenker's and vallecular diverticula. *Arch. Otolaryngol.* **96**, 171–175.

LAWSON R. S. (1957) Case of lingual thyroid with successful grafting after operative removal. *Aust. NZ J. Surg.* **26**, 241–243.

MONTGOMERY M. L. (1936) Lingual thyroid: a comprehensive review. *West. J. Surg.* **44**, 442–446.

O'DELL W. D., STEVENSON J. K. and WILLIAMS R. H. (1959) Treatment of a lingual goiter with Iri-iodothyronine. *J. Clin. Endocrinol. Metabol.* **19**, 363–368.

POTDAR G. C. and DESAI P. B. (1971) Carcinoma of the lingual thyroid. *Laryngoscope.* **81**, 427–429.

SCHILLING J. A., KARR J. W. and HURSH J. B. (1950) The treatment of a lingual thyroid with radioactive iodine. *Surgery* **27**, 130–138.

SWAN H., HARPER F. and CHRISTENSEN S. P. (1952) Autotransplantation of thyroid tissue in the treatment of lingual thyroid. *Surgery* **32**, 293–298.

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Post-surgical hyponatraemia: the role of intravenous fluids and arginine vasopressin

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SUMMARY

In 14 patients having undergone abdominal surgery, plasma sodium, urine volume and osmolality and the urinary excretion of arginine vasopressin (AVP), the antidiuretic hormone in man, were measured daily for 7 days. Each patient was given 3 l of intravenous fluids daily. In 8 patients the fluid was saline and in the other 6 it was dextrose-saline.

The plasma sodium did not change in the saline group whereas it fell in the dextrose–saline group during the day of operation and then remained low. On the day of operation the urinary AVP increased to very high levels in both groups of patients. On that day and during the postoperative period the AVP level and urine osmolality were much higher in the saline group than in the dextrose–saline group, which suggests that a loss or redistribution of extracellular fluid was not the cause of the high AVP. These results taken together suggest that it was the higher AVP level in the saline group that was required to keep the plasma sodium normal. On the other hand, the results suggest that in the dextrose–saline group, although the AVP was lower than in the saline group, it produced a urine osmolality greater than that necessary for balance so that the patients retained water and became hyponatraemic.

The fall in plasma sodium was small compared with that seen in patients with symptoms of water intoxication, but it may nevertheless have clinical effects and is best avoided. The results suggest that in these patients hyponatraemia can be avoided if saline rather than dextrose–saline is given on the day of operation.

PATIENTS after surgery are unable to excrete a water load as rapidly as before surgery and they become hyponatraemic if given too much dextrose solution intravenously (Le Quesne, 1954; Wynn, 1960). Dudley and his colleagues (1954) suggested that the failure to excrete the water was due to an excess of antidiuretic hormone, and increased levels of arginine vasopressin (AVP) in patients have been demonstrated by bioassay (Moran et al., 1964) and radioimmunoassay (Felsl et al., 1978; Haas and Glick, 1978). Patients after surgery have a diminished urinary excretion of sodium and they do not excrete all of a sodium load. This sodium retention has been attributed to a reduced plasma volume. Flear and Clark (1955) observed that sodium retention did not occur after trauma if the patients were given adequate blood transfusion. Irvin et al. (1972) reported that the urine sodium did not fall in patients after surgery if they were given balanced salt solution during as well as after the surgery. However, in the latter study the treatment did not prevent the excess ADH (as assessed by free water clearance), although it prevented the fall in plasma sodium seen in the patients given dextrose solution. This finding, which was not commented on by the authors, suggests that there is no simple relation between hyponatraemia and increased AVP.

The fall in plasma sodium which occurs in the majority of patients given dextrose or dextrose–saline after surgery is much smaller than that seen in patients with simple symptomatic water intoxication after surgery (Deutsch et al., 1966) or due to syntocinon (Morgan et al., 1977). However, there have been no studies designed to detect less obvious clinical effects in these patients showing small falls of plasma sodium, and until these investigations are made such falls in plasma sodium concentration are best avoided if possible. In order to obtain further information on the mechanism of this postoperative hyponatraemia we have studied the relations between plasma sodium, urine osmolality and AVP in patients having undergone surgery and given either saline or dextrose–saline intravenously.

Patients and methods

Fourteen patients were studied from the day before operation (day 0) until the seventh day after operation (day 7). The surgical procedures were cholecystectomy, vagotomy or hemicolectomy. The 8 patients in the saline group were given intravenously 3 l a day of saline containing 155 mmol/l of sodium chloride for 6 days beginning on the morning of the operation. The other 6 patients were given, for the same period, 3 l a day of dextrose–saline containing 278 mmol/l of glucose (4·3 per cent) and 30 mmol/l sodium chloride (0·18 per cent). A blood sample was taken each morning and 24-h urine collections were made for the 8 days of study (9.00 a.m. to 9.00 a.m.).

Plasma sodium was measured on a Vickers M300 multichannel analyser, urine osmolality was determined by freezing point depression on an Advance Osmometer and arginine vasopressin was measured in urine with a fully characterized radioimmunoassay (Thomas and Lee, 1976). The urinary excretion of AVP was expressed in terms of osmolar clearance (pg min^{-1} ml^{-1} osmolar clearance), and for the calculation of osmolar clearance, plasma osmolality was calculated as twice the plasma sodium concentration.

Results

Fig. 1 shows that the plasma sodium level was constant during the 8 days of the study in the saline group, whereas in the dextrose–saline group it fell by 5·9 mmol/l (range 3–11) after 1 day and by 7·1 mmol/l (range 5–11) after 2 days' treatment and then increased towards the preoperative value.

The maximum daily urine volume was similar in the two groups, but it was achieved on day 3 in the dextrose–saline group but not until day 6 in the saline group (*Fig.* 1). The osmolar excretion was two to three times greater in the saline group than in the dextrose–saline group. It was constant in the latter whereas in the saline group it increased to a maximum on day 5 (*Fig.* 1).

The urine osmolality was high throughout the study in the saline group whereas in the dextrose–saline

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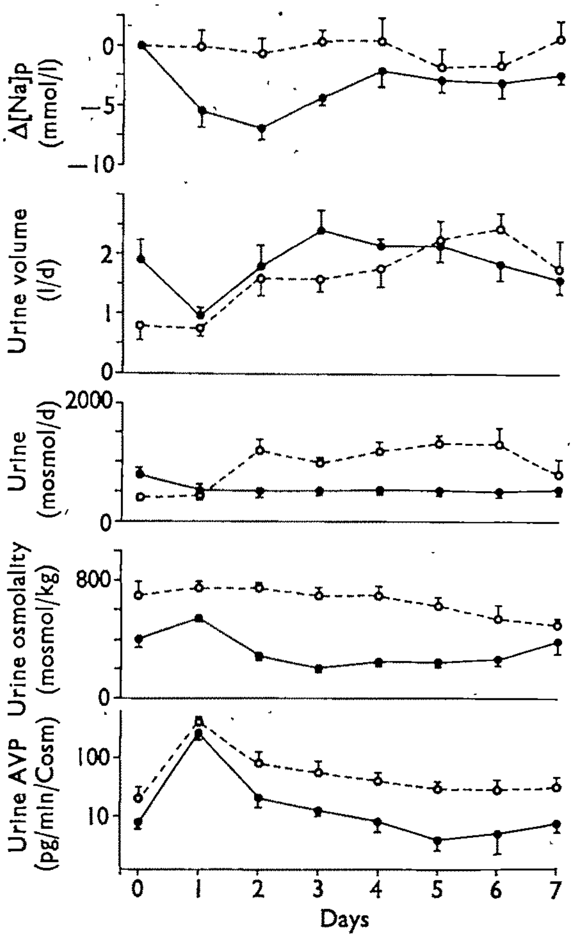

Fig. 1. The mean (±s.e.) values of plasma sodium concentration (as the difference from the value on day 0), urine volume, osmolar excretion, urine osmolality and urine arginine vasopressin (AVP) excretion on the day before operation (day 0), the day of operation (day 1) and for 6 days after operation (days 2–7) in 8 patients given intravenous saline (o——o) and 6 patients given intravenous dextrose–saline (●——●).

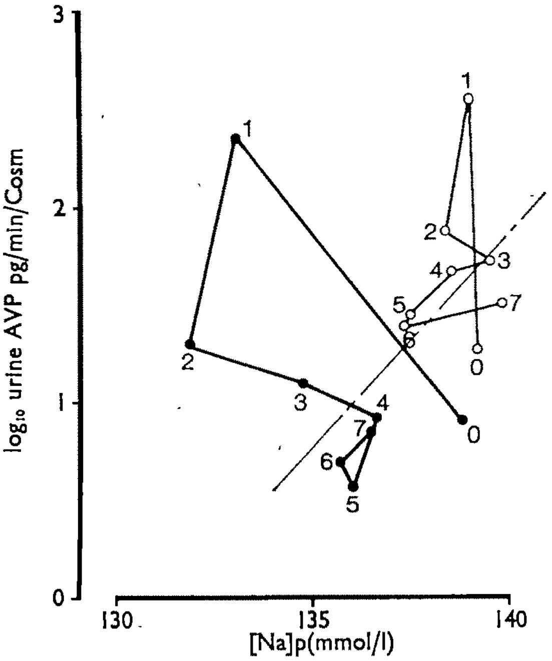

Fig. 2. The relationship between the mean values of plasma sodium concentration and urine arginine vasopressin (AVP) excretion on each day of study in 8 patients given intravenous saline (o——o) and 6 patients given intravenous dextrose–saline (●——●) postoperatively. The regression line is that observed in healthy subjects during water restriction (Thomas et al., 1978). Numbers against the points refer to the day of the study (day 1 was the day of operation).

group it was highest on the first day and then fell to a much lower value than that for the saline group (*Fig.* 1).

Fig. 1 shows the urine AVP results on a log scale. In both groups the urine AVP increased on the day of operation twentyfold compared with the preoperative values and then fell dramatically on the first postoperative day and more slowly on the subsequent days. However, throughout the postoperative period the AVP level in the saline group was four times that in the dextrose–saline group.

Fig. 2 shows that in the saline group, when all the results were taken together, the urine AVP was directly correlated with the plasma sodium concentration ($r = 0{\cdot}49$, $P < 0{\cdot}001$) and the mean daily values were close to the relationship observed in healthy persons deprived of water (Thomas et al., 1978). In contrast, in the dextrose–saline group, there was overall a negative correlation between the urine AVP level and the plasma sodium concentration ($r = 0{\cdot}40$, $P < 0{\cdot}05$). This negative correlation arose because the mean values for days 1, 2 and 3 were outside the relationship observed in healthy persons, with a much higher urine osmolality than would be expected for the plasma sodium.

Discussion

There has been no previous comparison of the effects of saline and dextrose–saline on plasma sodium concentration and antidiuretic hormone in patients after surgery. In the present study, on the day of operation the AVP increased in both groups of patients to levels which were much higher than those achieved by simple water depletion and much higher than would be expected from the plasma sodium concentration. On subsequent days the urine AVP was higher in the saline group, whose plasma sodium remained normal, than in the dextrose–saline group whose plasma sodium fell. These findings indicate that a suppression of AVP secretion was not the mechanism that prevented the fall in plasma sodium concentration in the saline group. They further suggest that a reduction in plasma volume or total extracellular fluid volume, which would have been diminished or corrected by the saline, was unlikely to be the cause of the increased AVP in either group. The initial increase in the AVP in both groups was therefore, presumably, a part of the stress response to the surgical operation (Moran et al., 1964).

In the saline group the plasma sodium concentration did not change during the 7 days of the study, and it must therefore have been the urine osmolality that was required to keep the plasma sodium normal. This finding suggests that in the saline group the AVP secretion was under osmotic control. In the dextrose–saline group the urine osmolality decreased after the first postoperative day to much lower values than in the saline group. Nevertheless, in the dextrose–saline group the urine osmolality on the first postoperative day must have been higher than was required for balance because the plasma sodium fell. The AVP in the dextrose–saline group must therefore have remained too high for the plasma osmolality so that the plasma AVP determined the plasma sodium rather than the other way round. These results therefore suggest that in the dextrose–saline group on the day of operation, the AVP was maintained by a non-osmolar stimulus at a level which produced an inappropriately high urine osmolality, water retention and a fall in plasma sodium due to a dilution of the extracellular fluid. Whereas the fall in plasma sodium may be due to simple dilution in patients such as ours, having undergone uncomplicated surgery (Wynn and Houghton, 1957; Singh and Flear, 1968), in some patients with complicated surgery part of the fall may be due to increased cellular permeability (Flear, 1970; Tindall and Clark, 1976).

Our general conclusion is that the stress of surgery maintained the AVP at a minimum level below which it could not be suppressed and that this minimum level determined the minimum obtainable urine osmolality. If a treatment was given that required for water balance a lower urine osmolality than this minimum, then water would be retained and the plasma sodium would fall. However, apart from this restriction, the osmolality control system is intact and urine osmolalities above this minimum could be produced as needed to maintain a normal plasma sodium.

We have calculated for our patients the minium requirements to maintain water balance and prevent the fall in plasma sodium. The calculation assumes that as the dextrose-treated patients were hyponatraemic they had no osmotic drive to AVP secretion. The fall in plasma sodium occurred on day 1 and calculations suggest that in order to prevent this fall, if 3 l of fluid were given, the fluid would have to contain at least 130 mmol/l of sodium chloride. Further calculations suggest that on days 2, 3 and 4, 3 l of only 20 mmol/l of sodium chloride could be given without a fall in plasma sodium. This was the treatment given to the dextrose group on those days and the plasma sodium did not fall. However, since this treatment was the requirement for balance, it did not allow the plasma sodium to increase from the low value it had already fallen to on day 1. The results suggest that in patients such as ours the fall in plasma sodium could be prevented by giving saline on day 1 and dextrose–saline on the subsequent days. In other groups of patients the AVP may remain high for longer than 1 day and dextrose–saline would then have to be avoided until the AVP fell to lower values.

The usual approach to fluid therapy after operation seems to be an attempt to ensure that the patient excretes the same volume of urine and amount of sodium as before operation. We suggest that in terms of water the choice of treatment should be based on what the patient can excrete without being overloaded.

The two groups of patients received the same volume of intravenous fluid and their urine volumes were similar, so that they retained similar volumes of water. Both groups not only had an increase in AVP due to the stress response, but would also have retained some of a sodium load (Moran et al., 1964). The patients in the dextrose–saline group became hyponatraemic because they were given water without sodium. The saline group retained sodium with water and the plasma sodium did not change. This sodium retention may well be due to a reduced plasma volume (Irvin et al., 1972; Enquist et al., 1978) but, as we have emphasized, a low plasma volume is unlikely to be the explanation of the increased AVP which causes the hyponatraemia in the patients given dextrose–saline.

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References

DEUTSCH S., GOLDBERG M. and DRIPPS R. D. (1966) Postoperative hyponatraemia with the inappropriate release of antidiuretic hormone. *Anaesthesiology* **27**, 250–256.

DUDLEY H. F., BOLING E. A., LE QUESNE L. P. et al. (1954) Studies on antidiuresis in surgery: effects of anaesthesia, surgery and posterior pituitary antidiuretic hormone on water metabolism in man. *Ann. Surg.* **140**, 354–365.

ENQUIST A., BLICHERT-TOFT M. and ØLGAARD K. (1978) Inhibition of aldosterone response to surgery by saline administration. *Br. J. Surg.* **65**, 224–227.

FELSL I., GOTTSMANN M., EVERSMANN T. et al. (1978) Influence of various stress situations on vasopressin secretion in man. *Acta Endocrinol* **87**, Suppl. 215, p. 122.

FLEAR C. T. G. (1970) Electrolyte and body water changes after trauma. *J. Clin. Pathol.* **23**, Suppl. 4, pp. 16–31.

FLEAR C. T. G. and CLARKE R. (1955) Influence of blood loss and blood transfusion upon changes in metabolism of water, electrolytes and civilian trauma. *Clin. Sci.* **14**, 575–599.

HAAS M. and GLICK S. M. (1978) Radioimmunoassayable plasma vasopressin associated with surgery. *Arch. Surg.* **113**, 597–600.

IRVIN T. T., HAYTER C. J., MODGILL V. K. et al. (1972) Plasma volume deficits and salt and water excretion after surgery. *Lancet* **2**, 1159–1161.

LE QUESNE L. P. (1954) Postoperative water retention with report of case of water intoxication. *Lancet* **2**, 172–174.

MORAN W. H., MILTENBERGER F. W., SHUAYB W. A. et al. (1964) The relationship of antidiuretic hormone secretion to surgical stress. *Surgery* **56**, 99–108.

MORGAN D. B., KIRWAN N. A., HANCOCK K. W. et al. (1977) Water intoxication and oxytocin infusion. *Br. J. Obstet. Gynaecol.* **84**, 6–12.

SINGH C. M. and FLEAR C. T. G. (1968) Why does the plasma sodium level fall after surgery? *Br. J. Surg.* **55**, 358.

THOMAS T. H., BALL S. G., WALES J. K. et al. (1978) Effect of Carbamazepine on plasma and urine arginine vasopressin *Clin. Sci. Mol. Med.* **54**, 419–424.

THOMAS T. H. and LEE M. R. (1976) The specificity of antisera for the radioimmunoassay of arginine-vasopressin in human plasma and urine during water loading and dehydration. *Clin. Sci. Mol. Med.* **51**, 525–536.

TINDALL S. F. and CLARK R. G. (1976) Hyponatraemia in surgical practice. *Br. J. Surg.* **63**, 150.

WYNN V. (1960) Some problems of water metabolism following surgery. In: STONER H. B. (ed.) *Biochemical Response to Injury*. Oxford, pp. 291–311.

WYNN V. and HOUGHTON B. J. (1957) Observations in man upon the osmotic behaviour of the body cell after trauma. *Q. J. Med.* **26**, 375–392.

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Effect of epidural analgesia on metabolic profiles during and after surgery

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SUMMARY

Blood concentrations of glucose, lactate, alanine, free fatty acids, glycerol and 3-hydroxybutyrate were measured during 24 h in 12 females undergoing elective hysterectomy under either general anaesthesia or epidural analgesia extending from T4 to S5. The results showed that the peroperative and immediate postoperative metabolic profiles in the group receiving general anaesthesia reflected substrate mobilization (increased glucose, lactate, 3-hydroxybutyrate), and that epidural analgesia blocked these changes, probably mediated through an inhibited adrenaline response to surgery. Peroperative values of free fatty acids and glycerol were significantly lowered by epidural analgesia, indicating inhibition of lipolysis. Alanine decreased similarly in both groups. In the later postoperative period metabolic profiles were similar in the two groups, indicating that the influence of fasting may override the effect of the relatively minor trauma.

BLOCKADE of afferent neurogenic stimuli from the surgical area by epidural analgesia inhibits various parameters of the endocrine response to surgery, such as cortisol (Engquist et al., 1977), growth hormone (Brandt, Kehlet, Binder et al., 1976) and aldosterone and renin (Brandt, Ølgaard et al., 1979), while postoperative changes in thyroid hormones (Brandt, Kehlet, Skovsted et al., 1976) are unaffected. Insulin secretion is probably slightly inhibited (Brandt, Kehlet and Binder, 1976; Brandt et al., 1977). Although the overall effect of epidural analgesia results in an improved postoperative nitrogen balance (Brandt, Fernandes et al., 1978), the influence on per- and postoperative metabolic profiles is unknown. In this study we describe the influence of epidural analgesia on postoperative changes in blood glucose, lactate, alanine, glycerol, free fatty acids (FFA) and 3-hydroxybutyrate.

Patients and methods

Twelve otherwise healthy and premenopausal women undergoing elective abdominal hysterectomy for menorrhagia or cancer of the cervix in stage 0–1 were studied during operation and for 24 h afterwards. Ages ranged from 27 to 47 years (average 36 years in the epidural group, and 38 years in the control group). All patients had a normal nutritional status (average weight 59·3±2·9 (s.e. mean) kg in the epidural group and 53·8±1·6 kg in the control group, $P>0·05$). All patients had a normal preoperative dietary intake, but they received no calories (oral or intravenous) from 10 h before to 24 h after skin incision. None of the patients suffered from cardiovascular, renal, hepatic or hormonal diseases nor received any medications, including hormonal contraceptives. Informed consent to participate in the study was obtained from all patients.

Six patients had general anaesthesia with thiopentone–halothane–nitrous oxide/oxygen, and 6 patients had epidural analgesia without general anaesthesia, using 0·5 per cent bupivacaine (Marcaine) without adrenaline. Analgesia, which extended from T4 to S5, was effective before skin incision and was controlled continuously during the following 24 h, constantly keeping the patients pain-free. Both groups were premedicated with pethidine 1 mg/kg, promethazine 12·5–25 mg and atropine 0·5 mg. A detailed description of the technique of general anaesthesia and epidural analgesia is reported elsewhere (Engquist et al., 1977). Operation started between 9 and 11 a.m. and required between 60 and 120 min (average 88 min in the epidural group and 93 min in the control group, $P>0·05$).

Patients operated under general anaesthesia received postoperative analgesia, 50 mg of pethidine every fourth to sixth hour, while patients operated under epidural analgesia were pain-free and had no other postoperative analgesia. During the first 24 postoperative hours, all patients received only isotonic saline intravenously and tap water orally. Twelve blood samples were drawn from a central venous catheter: 15 and 5 min before induction of anaesthesia or epidural analgesia, at skin incision and ½, 1, 2, 3, 4, 6, 9, 14 and 24 h after skin incision. Blood for metabolic estimations was deproteinized immediately after withdrawal by addition of 5 per cent (v/v) perchloric acid. Samples were centrifuged and stored at −21 °C within 20 min after sampling. Blood, blood substitutes or sympathomimetics were not given. Blood loss was similar (about 220 ml) in both groups. No patient had any postoperative complication.

Glucose was measured by a routine glucose oxidase method and lactate, alanine, glycerol and 3-hydroxybutyrate by enzymatic automated, fluorometric techniques (Lloyd et al., 1978) and FFA by a radioactive cobalt method (Ho and Meng, 1969). Cortisol was estimated by a protein-binding technique (Kehlet et al., 1974) and insulin (Heding, 1972) and growth hormone (Ørskov et al., 1968) by radioimmunoassays.

Student's *t* test for paired and unpaired data was used to test statistical significance. $P<0·05$ was considered significant.

Results

The results are summarized in *Figs.* 1–6.

Glucose

Blood glucose (*Fig.* 1) increased ($P<0·05$) immediately after skin incision in the control group and remained elevated ($P<0·05$) during the following 14 h. Epidural analgesia blocked the hyperglycaemic response to surgery throughout the study. Differences between groups were significant from 1 to 4 h and 9 h after skin incision.

Alanine

Blood alanine (*Fig.* 2) decreased ($P<0·05$) after surgery in both groups and remained lower than the preoperative value throughout the study. Except for lower values ($P<0·05$) in the epidural group 14 h after skin incision, there were no differences between the groups.

Lactate

Blood lactate (*Fig.* 3) was already increased ($P<0·05$) in the general anaesthesia group at the time of skin

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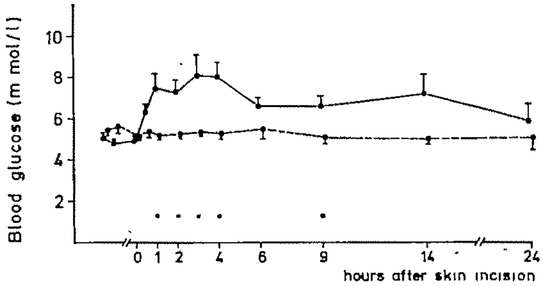

Fig. 1. Effect of epidural analgesia on glucose in blood during and after surgery. ●——●, General anaesthesia ($n = 6$); ● - - - ●, epidural analgesia ($n = 6$). Values are mean±s.e. mean. *$P<0{\cdot}05$.

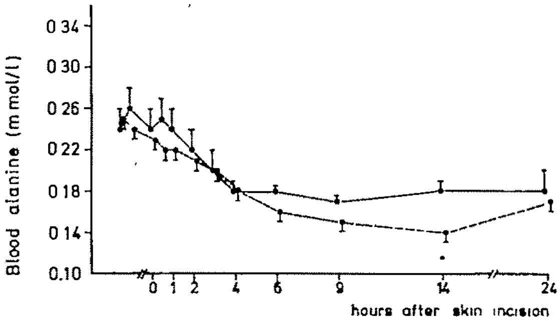

Fig. 2. Effect of epidural analgesia on alanine in blood during and after surgery. Symbols and numbers of cases as *Fig. 1*; values mean±s.e. mean.

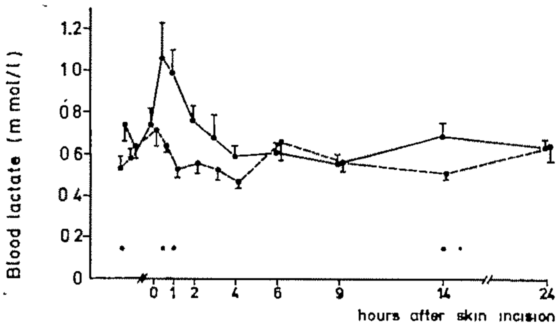

Fig. 3. Effect of epidural analgesia on lactate in blood during and after surgery. Symbols and numbers of cases as *Fig. 1*; values mean±s.e. mean.

incision and remained elevated during the following 3 h. In contrast, no changes in blood lactate were observed in the epidural group. Values were higher ($P<0{\cdot}05$) in the first preoperative sample in the epidural group, while 30 min and 1 and 14 h after skin incision values were higher ($P<0{\cdot}05$) in patients receiving general anaesthesia.

Glycerol

Blood glycerol (*Fig.* 4) showed no change in the general anaesthesia group while values decreased 1 h after skin incision in the epidural group. A difference ($P<0{\cdot}05$) between groups could only be detected 1 h after skin incision.

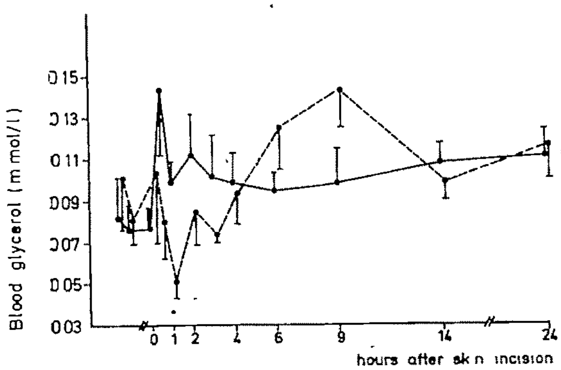

Fig. 4. Effect of epidural analgesia on glycerol in blood during and after surgery. Symbols and numbers of cases as *Fig.* 1; values mean±s.e. mean.

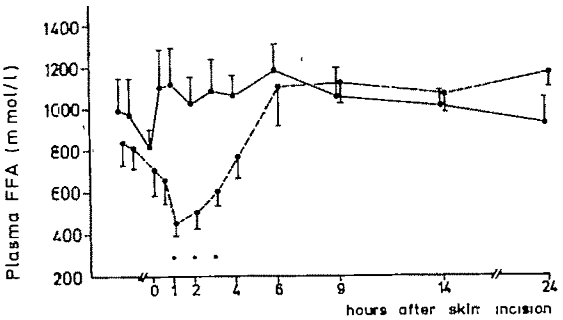

Fig. 5. Effect of epidural analgesia on free fatty acids (FFA) in plasma during and after surgery. Symbols and numbers of cases as *Fig.* 1; values mean±s.e. mean.

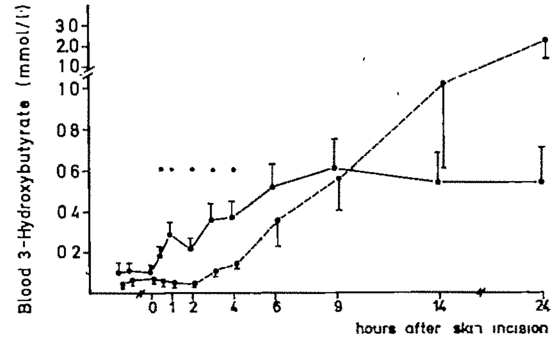

Fig. 6. Effect of epidural analgesia on 3-hydroxybutyrate in blood during and after surgery. Symbols and numbers of cases as *Fig.* 1; values mean±s.e. mean.

Free fatty acids (FFA)

Plasma FFA (*Fig.* 5) showed no significant change in the general anaesthesia group, while values decreased ($P<0{\cdot}05$) 1 h after skin incision in the epidural group. Mean values were lower ($P<0{\cdot}05$) 1–3 h after skin incision in the epidural group compared with the general anaesthesia group.

3-Hydroxybutyrate

Blood 3-hydroxybutyrate (*Fig.* 6) concentrations increased ($P<0{\cdot}05$) 30 min after skin incision in the general anaesthesia group and remained elevated throughout the study. In contrast, 3-hydroxybutyrate in the epidural group showed no changes until 4 h after skin incision, after which increased ($P<0.05$) values were observed. Differences between groups were significant from 30 min to 4 h after skin incision.

Cortisol, insulin and growth hormone

Plasma cortisol increased ($P<0.05$) immediately after skin incision in the general anaesthesia group from 246 ± 41 nmol/l (mean ± s.e. mean) before skin incision to a maximum of 1090 ± 57 nmol/l 3 and 6 h later and remained elevated ($P<0.05$) throughout the study compared with the preoperative value. Epidural analgesia blocked the cortisol response to surgery, the average concentrations being about 400–500 nmol/l throughout the study. Differences between groups were significant from 30 min to 9 h after skin incision. Plasma insulin decreased slightly ($P<0.05$) in the epidural group from 80 ± 20 pmol/l (mean ± s.e. mean) to 50 ± 20 pmol/l from the time of skin incision and throughout the study. In the general anaesthesia group values were not significantly changed from the preanaesthetic value (50 ± 20 pmol/l) except for a decrease 30 min after skin incision (20 ± 5 pmol/l). Differences between groups were not significant.

Plasma growth hormone increased ($P<0.05$) from 3·2 ± 1·4 ng/l (mean ± s.e. mean) to 17·4 ± 4·3 ng/l 30 min after skin incision in the general anaesthesia group, while no peroperative changes were observed in the epidural group. Differences between groups were significant 30 min and 1 h after skin incision. Postoperatively, patients under epidural analgesia showed intermittently very high values and no differences between groups were observed.

Discussion

The influence of neurogenic blockade by epidural analgesia on the endocrine response to surgery has recently been reviewed (Kehlet, 1978). It appears that epidural analgesia inhibits the normal per- and postoperative increase in cortisol, growth hormone, aldosterone, renin and adrenaline, the latter shown indirectly through an inhibited cyclic AMP response. Per- and postoperative changes in thyroxine and triiodothyronine as well as glucagon are not influenced by epidural analgesia, while insulin is slightly inhibited. This study considers initial per- and postoperative changes in metabolic profiles and their possible modifications by epidural analgesia.

Glucose

Our results confirm that the normal hyperglycaemic response to surgery is abolished by epidural analgesia (Bromage et al., 1971; Engquist et al., 1977). This effect is probably mediated through the inhibited adrenaline response or blockade of sympathetic pathways to the liver as discussed previously (Brandt, Kehlet, Binder et al., 1976).

Alanine

Alanine decreased rapidly after surgery, but similarly during general anaesthesia and epidural analgesia. The underlying mechanism behind the postoperative decrease in blood alanine, also demonstrated by others (Schønheyder et al., 1974; Wedge et al., 1976; Foster et al., 1979), is unknown. However, fasting may be a contributory factor, since blood alanine decreases during fasting due to an increased splanchnic uptake (Felig et al., 1969) despite a concomitantly increased release from muscle (Pozetsky et al., 1976). In severe trauma, i.e. burns, elevated blood levels of alanine have been observed (Batstone et al., 1976) and thought to be secondary to increased cortisol levels since glucocorticoids increase blood alanine (Wise et al., 1973). However, during elective surgery other mechanisms may regulate alanine homeostasis since alanine levels were decreasing similarly during general anaesthesia and epidural analgesia despite a pronounced difference in cortisol levels.

Lactate

Blood lactate increased during general anaesthesia and surgery, as found by others (Greene, 1961), but values were normal postoperatively, which is again in agreement with others (Rowlands et al., 1977; Foster et al., 1979). That the peroperative increase in lactate is partly mediated via the anaesthetic agent itself (Greene, 1961) is confirmed by our results showing a rise in lactate at the time of skin incision. However, the surgically induced adrenaline release (Halter et al., 1977; Nistrup Madsen et al., 1978) may also result in a rise in blood lactate (Christensen et al., 1975). The constant lactate levels during epidural analgesia are in accordance with the blocked adrenaline response and the omission of general anaesthesia.

Glycerol and FFA

The surgical procedure may initiate an increase in blood glycerol and FFA (Hallberg and Orö, 1965), probably as a result of increased lipolysis due to catecholamine release. Our results showed only an insignificant increase in glycerol and FFA after skin incision in the general anaesthesia group, but during epidural analgesia and surgery levels of both metabolites decreased rapidly in accordance with the inhibited catecholamine secretion. Similar observations have been made during spinal anaesthesia (Hallberg and Orö, 1965). In contrast, Oyama and Matsuki (1970) found spinal anaesthesia to have no influence on plasma FFA, but their patients had varying and very minor surgery. Furthermore, postoperative determinations were made, by which time analgesia was ineffective.

3-Hydroxybutyrate

Surgery performed under general anaesthesia elicited an increase in 3-hydroxybutyrate immediately after skin incision, probably as a result of release of adrenaline, which is known to increase blood 3-hydroxybutyrate (Christensen et al., 1975). However, growth hormone and cortisol may also contribute to the ketogenic response during the postoperative phase with relative insulin deficiency (Alberti et al., 1978). In accordance with the blocked adrenaline response, epidural analgesia inhibited the surgically induced increase in 3-hydroxybutyrate, but levels began to increase 4 h after skin incision, probably due to the influence of fasting (Foster et al., 1979).

In summary, epidural analgesia blocked the changes in blood metabolic profiles induced by the surgical procedure, predominantly mediated through an inhibited adrenaline response to surgery. Postoperative metabolic profiles were mainly unaffected by epidural analgesia, except for the lack of hyperglycaemia, probably reflecting that the influence of starvation may override the metabolic response to such relatively minor trauma as hysterectomy. The inhibited cortisol and growth hormone response to surgery during epidural analgesia probably did not have any major influence on per- and early postoperative changes in the intermediary metabolic profiles in blood, since these hormones have no major acute effects on glucose, FFA and 3-hydroxybutyrate (Marco et al., 1973; Fineberg and Merimee, 1974; Schade et al., 1977). Neither did the slight decrease in insulin during epidural analgesia seem to be of importance, except as a contributory factor to postoperative ketogenesis. Despite the apparently short term effects of epidural analgesia on the surgically induced changes in the various endocrine–metabolic parameters in blood found in this study, a longer lasting effect on metabolic balance has been demonstrated by means of an improved 5-day postoperative nitrogen balance (Brandt, Fernandes et al., 1978). However, since metabolic and endocrine profiles in this latter study were only measured during the first 24 h, the explanation of the sustained effect of epidural analgesia on postoperative metabolism is unclear.

References

ALBERTI K. G. M. M., JOHNSTON D. G., GILL A. et al. (1978) Hormonal regulation of ketone body metabolism in man. In: GARLAND P. and HALES C. N. (ed.) *Substrate Mobilization and Energy Provision in Man. Biochem. Soc. Symp.* **43**, 163–182.

BATSTONE G., ALBERTI K. G. M. M., HINKS L. et al. (1976) Metabolic studies in subjects following thermal injury. *Burns* **2**, 207–225.

BRANDT M. R., FERNANDES A., MORDHORST R. et al. (1978) Epidural analgesia improves postoperative nitrogen balance. *Br. Med. J.* **1**, 1106–1108.

BRANDT M. R., KEHLET H., BINDER C. et al. (1976) Effect of epidural analgesia on the glucoregulatory endocrine response to surgery. *Clin. Endocrinol.* **5**, 107–114.

BRANDT M. R., KEHLET H., FABER O. et al. (1977) C-peptide and insulin during blockade of the hyperglycemic response to surgery by epidural analgesia. *Clin. Endocrinol.* **6**, 167–170.

BRANDT M. R., KEHLET H., SKOVSTED L. et al. (1976) Rapid decrease in plasma tri-iodothyronine during surgery and epidural analgesia independent of afferent neurogenic stimuli and of cortisol. *Lancet* **2**, 1333–1336.

BRANDT M. R., ØLGAARD K. and KEHLET H. (1979) Epidural analgesia blocks the renin and aldosterone response to surgery. *Acta Anaesth. Scand.* (In the press.)

BROMAGE P. R., SHIBATA H. R. and WILLOUGHBY H. W. (1971) Influence of prolonged epidural blockade on blood sugar and cortisol responses to operations upon the upper part of abdomen and the thorax. *Surg. Gynecol. Obstet.* **132**, 1051–1056.

CHRISTENSEN N. J., ALBERTI K. G. M. M. and BRANDSBORG O. (1975) Plasma catecholamines and blood substrate concentrations: studies in insulin induced hypoglycemia and after adrenaline infusions. *Eur. J. Clin. Invest.* **5**, 415–423.

ENGQUIST A., BRANDT M. R., FERNANDES A. et al. (1977) The blocking effect of epidural analgesia on the adrenocortical and hyperglycemic responses to surgery. *Acta Anaesth. Scand.* **21**, 330–335.

FELIG P., OWEN O. E., WAHREN J. et al. (1969) Amino acid metabolism during prolonged starvation. *J. Clin. Invest.* **48**, 584–594.

FINEBERG S. E. and MERIMEE T. J. (1974) Acute metabolic effects of human growth hormone. *Diabetes* **23**, 499–504.

FOSTER K. J., ALBERTI K. G. M. M., BINDER C. et al. (1979) Lipid metabolites and nitrogen balance after abdominal surgery in man. *Br. J. Surg.* **66**, 242–245.

GREENE N. M. (1961) Lactate, pyruvate and excess lactate production in anesthetized man. *Anesthesiology* **22**, 404–412.

HALLBERG D. and ORÓ L. (1965) Free fatty acids of plasma during spinal anaesthesia in man. *Acta Chir. Scand.* **178**, 281–290.

HALTER J. B., PFLUG A. E. and PORTE D. jun. (1977) Mechanism of plasma catecholamine increases during surgical stress in man. *J. Clin. Endocrinol. Metabol.* **45**, 936–944.

HEDING L. (1972) Determination of total serum insulin (IRI) in insulin-treated diabetic patients. *Diabetologia* **8**, 260–266.

HO R. J. and MENG H. C. (1969) A simple and ultrasensitive method for determination of free fatty acids by radiochemical assay. *Analyt. Chem.* **31**, 426–436.

KEHLET H. (1978) Influence of epidural analgesia on the endocrine-metabolic response to surgery. *Acta Anaesth. Scand.* Suppl. 70, pp. 39–42.

KEHLET H., BINDER C. and ENGBAEK C. (1974) Cortisol binding capacity during anaesthesia and surgery. *Acta Endocrinol.* **75**, 119–124.

LLOYD B., BURRIN J., ALBERTI K. G. M. M. et al. (1978) Simple automated enzymic fluorimetric assays for blood glucose, lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate. *Clin. Chem.* **24**, 1724–1729.

MARCO J., CALLE C., ROMAIN D. et al. (1973) Hyperglucagonism induced by glucocorticoid treatment in man. *N. Engl. J. Med.* **288**, 128–131.

NISTRUP MADSEN S., FOG-MØLLER F., CHRISTIANSEN C. et al. (1978) Cyclic AMP, adrenaline, and noradrenaline in plasma during surgery. *Br. J. Surg.* **65**, 191–193.

ØRSKOV H., THOMPSON H. G. and YDE H. (1968) Wick chromatography for rapid and reliable immunoassay of insulin, glucagon, and growth hormone. *Nature (Lond.)* **219**, 193–195.

OYAMA T. and MATSUKI A. (1970) Effects of spinal anaesthesia and surgery on carbohydrate and fat metabolism in man. *Br. J. Anaesth.* **42**, 723–729.

POZEFSKY T., TANCREDI R. G., MOXLEY R. T. et al. (1976) Effects of brief starvation on muscle amino acid metabolism in non-obese man. *J. Clin. Invest.* **57**, 444–449.

ROWLANDS B. J., GIDDINGS A. E. B. and CLARK R. G. (1977) Changes in plasma lactate, phosphate and uric acid during postoperative carbohydrate infusion. *Br. J. Surg.* **64**, 424–427.

SCHADE D. S., EATON R. P. and STANDEFER J. (1977) Glucocorticoid regulation of plasma ketone body concentration in insulin deficient man. *J. Clin. Endocrinol. Metabol.* **44**, 1069–1079.

SCHØNHEYDER F., BONÉ J. and SKJOLDBORG H. (1974) Variations in plasma amino acid concentrations after abdominal surgical procedures. *Acta Chir. Scand.* **140**, 271–275.

WEDGE J. H., DE CAMPOS R., KERR A. et al. (1976) Branched chain amino acids, nitrogen excretion and injury in man. *Clin. Sci. Mol. Med.* **50**, 393–399.

WISE J. K., HENDLER R. and FELIG P. (1973) Influence of glucocorticoids on glucagon secretion and plasma amino acid concentrations in man. *J. Clin. Invest.* **52**, 2774–2782.

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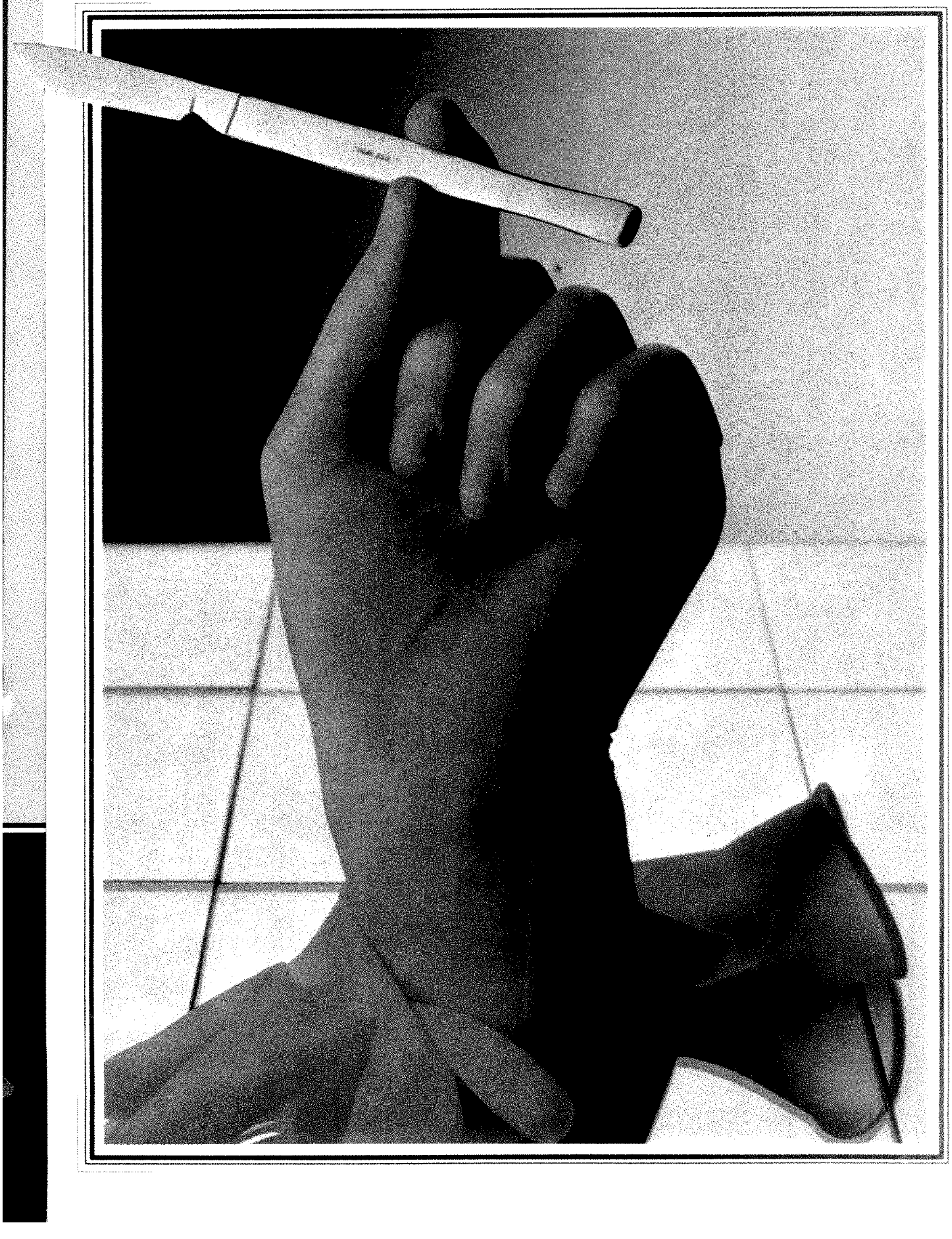

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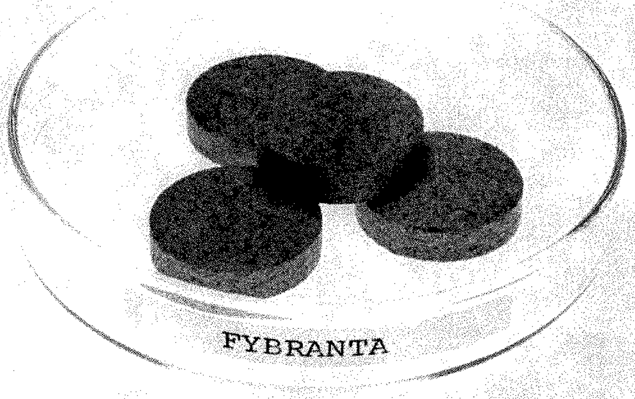

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Br. J. Surg. Vol. 66 (1979) 547–549

Postprandial serum gastrin levels in patients with combined hypergastrinaemia and hyperchlorhydria

C. B. H. LAMERS AND J. H. M. VAN TONGEREN*

SUMMARY

We have determined the serum gastrin response to a standard test meal in 13 unoperated patients with combined fasting hypergastrinaemia (more than 150 ng/l) and basal hypersecretion of gastric acid (BAO more than 10 mmol/h). In 10 of 11 patients with proved or presumptive Zollinger–Ellison syndrome the peak postprandial rise in serum gastrin concentration was less than 50 per cent of basal value. The integrated gastrin response to feeding ranged from −71·9 to 211·8 μg/l× 150 min. In 2 patients with proved hypergastrinaemia of antral origin, however, serum gastrin rose to 223 per cent and 255 per cent respectively of basal value after ingestion of the meal. The integrated postprandial serum gastrin responses in these patients were 66·8 and 22·0 μg/l×150 min. Two patients with Zollinger–Ellison syndrome and total gastrectomy showed peak serum gastrin levels after feeding of 174 and 255 per cent of basal concentration. The integrated postprandial gastrin secretions were 365 and 366 μg/l×150 min respectively.

It is concluded that the serum gastrin response to feeding, when expressed as percentage change, may be helpful in the differential diagnosis of unoperated patients with fasting hypergastrinaemia and basal gastric acid hypersecretion.

INGESTION of food is a physiological stimulus for the release of gastrin from the mucosa of the antrum and duodenum (Berson and Yalow, 1972). The postprandial rise in serum gastrin is therefore considered to be an indirect test of the gastrin-cell function of the gastroduodenal mucosa.

In patients with combined fasting hypergastrinaemia and basal hyperchlorhydria, elevated serum gastrin concentrations may arise either from the antral mucosa (primary hypergastrinaemia of antral origin) or from extra-gastric sources (Zollinger–Ellison syndrome) (Berson and Yalow, 1972; Isenberg et al., 1973; Walsh and Grossman, 1975). It has been suggested that the serum gastrin response to feeding is helpful in the differentiation between these two sources of hypergastrinaemia (Berson and Yalow, 1972). This differentiation is based upon the supposition that feeding stimulates gastrin release from the antroduodenal mucosa but not from gastrin-producing tumours (Isenberg et al., 1973). Recent studies, however, have shown that some of the patients with Zollinger–Ellison syndrome show large postprandial rises in serum gastrin (Creutzfeldt et al., 1975; Thompson et al., 1975). Unfortunately, many patients in those studies had undergone previous gastric or pancreatic surgery.

In view of conflicting data on postprandial serum gastrin levels in the limited reported number of unoperated patients with combined fasting hypergastrinaemia and basal gastric acid hypersecretion (Berson and Yalow, 1972; Creutzfeldt et al., 1975; Thompson et al., 1975), we report on the serum gastrin response to feeding in 13 such patients. Three had histologically proved Zollinger–Ellison syndrome, 8 presumptive Zollinger–Ellison syndrome and 2 hypergastrinaemia of antral origin. Furthermore, 2 of the patients with Zollinger–Ellison syndrome were studied after total gastrectomy.

Patients and methods

All patients included in this study had fasting hypergastrinaemia (a level of more than 150 ng/l) and basal hypersecretion of gastric acid (BAO more than 10 mmol/h). Except for the 2 patients with total gastrectomy, none had undergone previous gastric or pancreatic surgery. Three patients in whom the Zollinger–Ellison syndrome was histologically proved at a later date had fasting serum gastrin levels ranging from 1240 to 5800 ng/l and a BAO of between 17·0 and 57·5 mmol/h. The diagnosis of presumptive Zollinger–Ellison syndrome was based upon a rise in serum gastrin of more than 50 per cent of basal value within 30 s of intravenous administration of 1 unit secretin (from the Gastrointestinal Hormone Research Laboratory, Karolinska Institute, Stockholm), per kilogramme body weight (Lamers et al., 1977). In these 8 patients serum gastrin ranged from 170 to 780 ng/l with a BAO of between 15·1 and 67 mmol/h. The 2 patients with primary hypergastrinaemia of antral origin had serum gastrin concentrations of 160 and 415 ng/l and BAOs of 11·3 and 11·0 mmol/h respectively. Both serum gastrin (36 and 67 ng/l) and BAO (0 and 0·7 mmol/h) returned to normal after antrectomy. The 2 Zollinger–Ellison syndrome patients studied after total gastrectomy had serum gastrin concentrations of 3280 and 5130 ng/l at the time of study.

After an overnight fast the subjects ingested a standard test meal within 15 min. This meal consisted of one slice of bread, 50 g cheese, one boiled egg and 200 ml milk, corresponding to 30 g protein, 20 g fat and 25 g carbohydrate. Before and 15, 30, 45, 60, 90, 120 and 150 min after the start of the meal blood was drawn for measurement of gastrin.

Serum gastrin levels were measured by radioimmunoassay using a rabbit antiserum (Lamers et al., 1977). The antiserum was raised against synthetic human gastrin I containing amino acid residues 2–17, conjugated to bovine albumin (Rehfeld et al., 1972). It had an almost equimolar potency to bind gastrin-17 and gastrin-34 (Rehfeld et al., 1975). Serum gastrin levels in 100 normal controls were 66±18 ng/l (mean±s.d.). The integrated serum gastrin response to feeding was determined by calculating the area under the curve after subtraction of the basal gastrin concentration. Ingestion of the standard test meal in 12 normal subjects induced an increase in serum gastrin from 52±12 ng/l (mean±s.d.) to a peak of 97±33 ng/l at 60 min. The integrated gastrin response to feeding in these 12 normal subjects was 5·2±2·9 μg/l × 150 min (Lamers, 1977).

Statistical analysis was performed by Wilcoxon's two-sample test.

Results

Two of the 3 patients with histologically proved Zollinger–Ellison syndrome had a slight postprandial rise in serum gastrin, while the other patient showed a small decrease in circulating gastrin levels (*Fig.* 1). In none of the patients did the postprandial increase in serum gastrin exceed 50 per cent of the basal value. The integrated postprandial gastrin secretion was −71·9, 24·7 and 211·8 μg/l × 150 min respectively.

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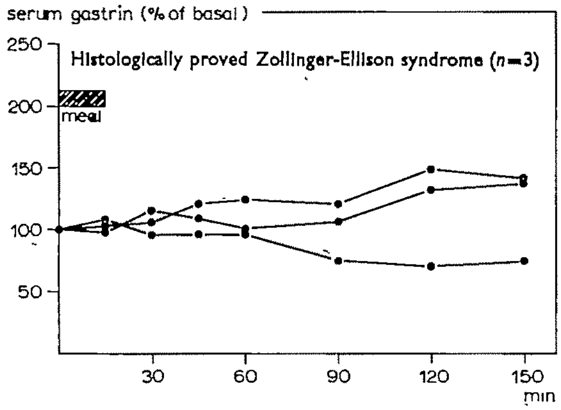

Fig. 1. Postprandial serum gastrin levels in patients with histologically proved Zollinger–Ellison syndrome.

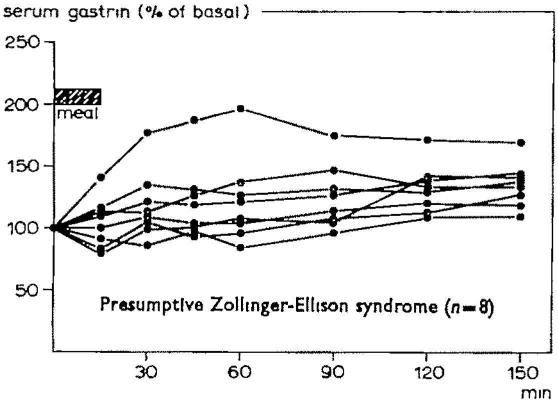

Fig 2. Postprandial serum gastrin levels in patients with presumptive Zollinger–Ellison syndrome.

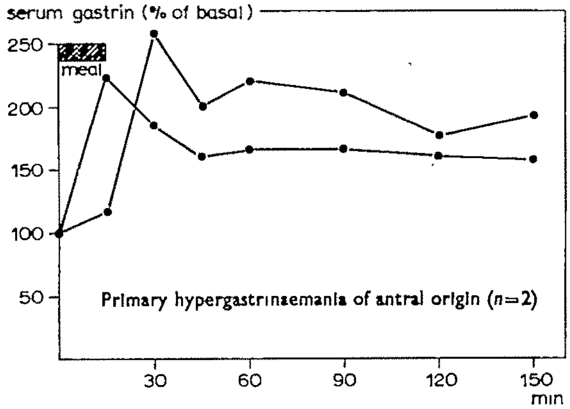

Fig. 3. Postprandial serum gastrin levels in patients with primary hypergastrinaemia of antral origin.

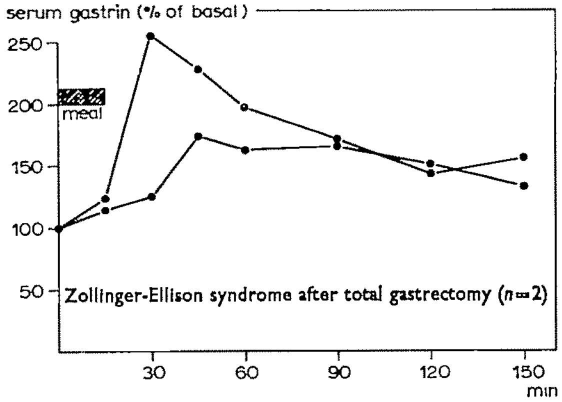

Fig. 4. Postprandial serum gastrin levels in patients with Zollinger–Ellison syndrome having undergone total gastrectomy.

Seven of the 8 patients with presumptive Zollinger–Ellison syndrome had slight postprandial increases in serum gastrin of less than 50 per cent of the basal value (*Fig.* 2). In one patient, however, serum gastrin almost doubled after ingestion of the test meal. In this group of patients serum gastrin concentrations at 90, 120 and 150 min were significantly ($P<0{\cdot}05$) elevated above basal level. The integrated gastrin response to feeding ranged from 3·9 to 81·3 μg/l × 150 min with a median of 9·8 μg/l × 150 min.

Two patients with hypergastrinaemia of antral origin showed a rise in serum gastrin of more than 120 per cent of basal value (*Fig.* 3). The integrated postprandial gastrin responses in these patients were 22·0 and 66·8 μg/l × 150 min respectively.

The 2 patients with Zollinger–Ellison syndrome who had undergone total gastrectomy showed marked postprandial increases in serum gastrin to 174 and 255 per cent of basal value respectively (*Fig.* 4). The integrated gastrin responses to feeding were 365 and 366 μg/l × 150 min.

Discussion

The present study shows that postprandial rises in serum gastrin in 10 of 11 patients with proved or presumptive Zollinger–Ellison syndrome were less than 50 per cent of basal value. On the other hand, the two patients with proved hypergastrinaemia of antral origin had postprandial increases in serum gastrin of more than 120 per cent. The possibility that the patient with presumptive Zollinger–Ellison syndrome and a marked postprandial rise in serum gastrin was in fact suffering from hypergastrinaemia of antral origin was excluded by the finding of persistent hypergastrinaemia after total gastrectomy. Although the number of patients with hypergastrinaemia of antral origin in the present study is small, the results are supported by data on postprandial serum gastrin levels in patients with presumed or proved hypergastrinaemia of antral origin studied by others (Berson and Yalow, 1972; DiMagno and Go, 1974; Straus and Yalow, 1975). It can therefore be concluded that the finding of marked postprandial increases in serum gastrin should raise the suspicion of hypergastrinaemia of antral origin, although the Zollinger–Ellison syndrome cannot be excluded with certainty. Furthermore, the serum gastrin response to secretin may also be helpful in the differential diagnosis of these patients. Since not every case of Zollinger–Ellison syndrome shows a marked gastrin response to intravenous secretin (Lamers et al., 1977), both the meal and the secretin stimulation test should be done to obtain optimal diagnostic information.

The integrated gastrin response to feeding in some patients with Zollinger–Ellison syndrome was much greater than in normal controls. We cannot, therefore, exclude the possibility that some of the gastrin released after feeding in such patients originates from gastrinoma tissue. This suggestion is supported by the finding of large postprandial increases in serum gastrin in 2 cases with Zollinger–Ellison syndrome after total gastrectomy. This marked gastrin response to feeding has been described previously in a larger group of totally gastrectomized patients with the syndrome (Thompson et al., 1975). These authors suggested that the postprandial release of gastrin in such patients was mediated by a humoral factor. Passaro and Walsh (1977) showed that perfusion of the proximal duodenum with acid, peptone or alcohol in totally gastrectomized patients with Zollinger–Ellison syndrome led to marked increases in serum gastrin. These authors therefore postulated that a duodenal agent, other than secretin, causes the release of gastrin from gastrinoma.

It can be concluded that measurement of postprandial serum gastrin has some, although limited, significance in the differential diagnosis of unoperated patients with fasting hypergastrinaemia and basal hypersecretion of gastric acid. Obviously, studies in larger groups of patients are needed to elucidate further the discriminative potency of meal stimulation tests in such patients.

References

BERSON S. A. and YALOW R. S. (1972) Radioimmunoassay in gastroenterology. *Gastroenterology* **62**, 1061–1084.

CREUTZFELDT W., ARNOLD R., CREUTZFELDT C. et al. (1975) Pathomorphologic, biochemical and diagnostic aspects of gastrinomas (Zollinger–Ellison syndrome). *Hum. Pathol.* **6**, 47–76.

DIMAGNO E. P. and GO V. L. W. (1974) Malabsorption secondary to antral gastrin-cell hyperplasia. *Mayo Clin. Proc.* **49**, 727–730.

ISENBERG J. I., WALSH J. H. and GROSSMAN M. I. (1973) Zollinger–Ellison syndrome. *Gastroenterology* **65**, 140–165.

LAMERS C. B. H. W. (1977) Fasting and postprandial serum gastrin levels in normal subjects, duodenal ulcer patients and patients with partial or total gastrectomy. *Neth. J. Med.* **20**, 238 (Abstr.).

LAMERS C. B., BUIS J. T. and VAN TONGEREN J. H. (1977) Secretin-stimulated serum gastrin levels in hyperparathyroid patients from families with multiple endocrine adenomatosis type I. *Ann. Intern. Med.* **86**, 719–724.

PASSARO E. and WALSH J. H. (1977) Release of gastrin from gastrinomas by protein in duodenum. *Gastroenterology* **72**, 820 (Abstr.).

REHFELD J. F., STADIL F., MALMSTRÖM J. et al. (1975) Gastrin heterogeneity in serum and tissue. In: THOMPSON J. C. (ed.) *Gastrointestinal Hormones*. Austin, University of Texas Press, pp. 43–58.

REHFELD J. F., STADIL F. and RUBIN B. (1972) Production and evaluation of antibodies for the radioimmunoassay of gastrin. *Scand. J. Clin. Lab. Invest.* **30**, 221–232.

STRAUS E. and YALOW R. S. (1975) Differential diagnosis of hypergastrinemia. In: THOMPSON J. C. (ed.) *Gastrointestinal Hormones*. Austin, University of Texas Press, pp. 99–113.

THOMPSON J. C., REEDER D. D., VILLAR H. V. et al. (1975) Natural history and experience with diagnosis and treatment of the Zollinger–Ellison syndrome. *Surg. Gynecol. Obstet.* **140**, 721–739.

WALSH J. H. and GROSSMAN M. I. (1975) Gastrin. *N. Engl. J. Med.* **292**, 1377–1384.

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Br. J. Surg. Vol. 66 (1979) 550–551

Prolonged post-vagotomy gastric atony treated by oxytocin

M. HASHMONAI, S. TOREM, S. ARGOV, A. BARZILAI AND A. SCHRAMEK*

SUMMARY

Persistent and complete post-vagotomy gastric atony was treated in 3 patients by intravenous infusion of oxytocin. Despite failure of both conventional treatment with gastric aspiration and intravenous fluids or jejunal feeding, as well as the reported trials with bethanechol chloride and metoclopramide, these patients promptly responded to oxytocin. It appears that the latter may represent a solution to this uncommon but recalcitrant complication of peptic ulcer surgery.

SEVERE gastric atony is an unusual but well-recognized complication of vagotomy with a drainage procedure. It is due to a motor dysfunction of the stomach resulting in absence of peristalsis. Thus, although an adequate anatomic outlet exists, stomach emptying does not take place. Despite treatment by gastric aspiration and parenteral or jejunal feeding, this condition may persist for a long period, even months.

The purpose of this study is to present a new pharmacological approach to this problem—the use of intravenous oxytocin.

Patients and methods

Three young male patients were studied. Each had a duodenal ulcer complicated by pyloric stenosis. They had been suffering from epigastric pain for 7–16 years. Two of them had bled from their ulcers. All three had been vomiting, one for the past 3 years, one for 1½ years and the third for 5 months. Upper gastrointestinal barium studies performed before surgery showed a duodenal ulcer with a severely deformed and narrowed pyloric canal with slow emptying of a moderately (in the first and second cases) and severely (in the third case) dilated stomach. In all, a truncal vagotomy and Jaboulay gastroduodenostomy were performed. Two of the patients had an apparently uneventful recovery and were discharged on the eighth postoperative day. One week later both were readmitted because of epigastric fullness and vomiting. The third patient developed the same complaints in the immediate post-postoperative period.

Barium meal examinations showed a grossly dilated, persistently aperistaltic stomach in each case. Very limited gastric emptying was demonstrated in certain postures only by the gravitational flow of barium through the anastomosis, which was wide and patent. Plain abdominal X-rays, performed 24 h later, showed that most of the barium was still in the stomach. In 2 cases, patency of the anastomosis was confirmed on gastroscopy.

The first patient was treated by persistent nasogastric aspiration and total parenteral alimentation. The other 2 patients were treated by aspiration via a gastrostomy and by tube jejunal feeding. However, repeated barium fluoroscopic examinations showed that the stomach had not recovered its motility and no significant reduction in the amount of gastric aspiration occurred (*Fig.* 1). An attempt to treat the first patient with metoclopramide and bethanechol chloride 3 months after his operation failed. After the gastric atony had persisted for 4 months in the first case and for 2 months in the other two, oxytocin treatment was started. An intravenous infusion of 5–20 units of oxytocin in 500 ml of normal saline was administered every 4 h for 3 days. Each patient was submitted to a fluoroscopic barium examination immediately before the onset of this treatment. The stomach was found to be, as in all previous examinations, completely atonic, lacking any peristaltic movement and rather distended despite the persistent gastric aspiration. Twenty to thirty minutes after onset of the oxytocin infusion, some contractions of the stomach appeared. Repeated barium meals performed after 3 days of treatment showed effective gastric contractions in one case, partially effective contractions in another and only some reversed peristaltic waves in the third patient. In the latter case, oxytocin was continued for 3 additional days, after which effective peristalsis of the stomach was achieved. A concomitant drastic decrease in the amount of gastric aspirate was also observed (*Fig.* 1). After the oxytocin was discontinued, the gastric aspiration was maintained for another day and, as no rise in the amount was recorded, the tubes were taken out and the patients were placed on a normal diet. A barium meal performed 3 weeks later showed effective contractions of the stomach with complete emptying within 90–120 min.

The side effects of this treatment were colicky abdominal pain, mainly in the epigastrium, and some bouts of diarrhoea. These were overcome by reducing the dosage of oxytocin.

Discussion

Despite the introduction of selective and highly selective vagotomy, truncal vagotomy with a drainage procedure is still the commonest surgical treatment for peptic ulcer. Gastric motility is always disturbed after any type of vagotomy, but particularly after the truncal section of the vagi (Sheiner and Catchpole, 1976). Pyloroplasty slightly slows the rate of gastric emptying. When a vagotomy is performed, the gastric motility is considerably slower than normal and when a pyloroplasty is added, although much enhanced, gastric emptying is still slower than normal (Edwards and Rowlands, 1968). This disturbance is caused by a complex alteration of gastric motor function. In the normal stomach, the major muscular activity promoting emptying is phasic synchronized peristalsis. The major muscular activity promoting gastric emptying after vagotomy is tonic pressure change plus poorly synchronized abbreviated phasic activity (Nelsen et al., 1967). Yet, in the majority of patients, no significant clinical symptoms persist. This is probably due to the partial restoration of gastric motility through a peripheral motor mechanism controlled by the Auerbach's plexus (Dragstedt et al., 1947). The cause for the complete gastric atony that is occasionally observed following vagotomy is still obscure (Donovan and Alexander-Williams, 1976), but it may be associated with previous gastric distension due to pyloric stenosis, as reported in the majority of the cases in the literature (Bergin and Jordan, 1959; Vasconez et al., 1970; Sheiner and Catchpole, 1976). Indeed, gastric atony was observed in 5 per cent of patients following vagotomy with a drainage procedure for non-obstructing duodenal ulcer and in 27 per cent of cases having a similar procedure for pyloric obstruction (Kraft et al., 1964). It seems that this is a cumulative result of previous chronic gastric distension plus autonomic gastric motor denervation (Kraft et al., 1964). All three of our cases had pyloric stenosis complicating their peptic ulcer.

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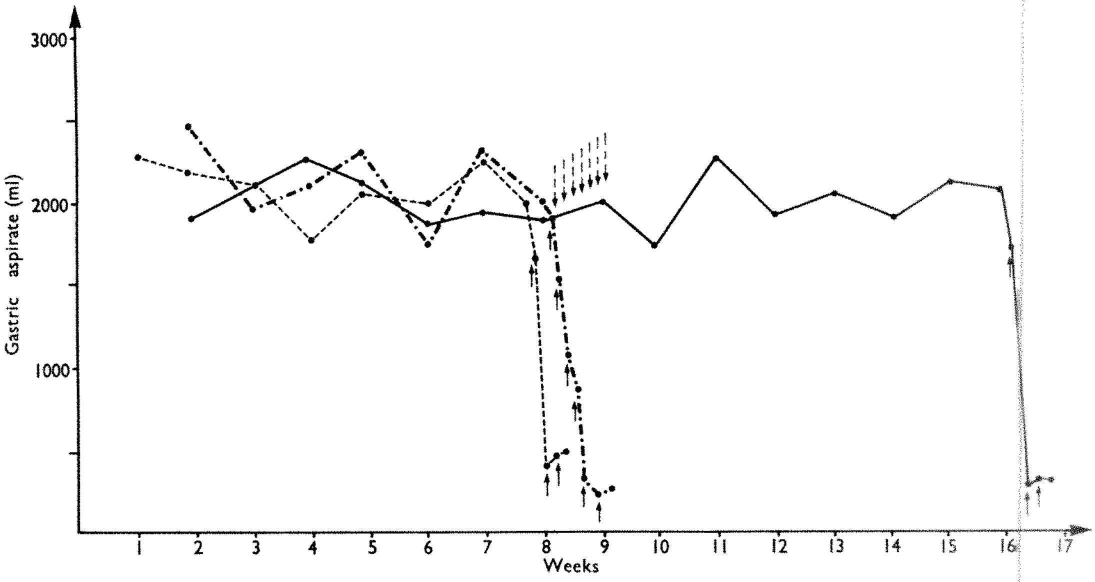

Fig. 1. Gastric aspirate curves. Arrows point to the days on which oxytocin was given. Dotted arrows point to the days on which bethanechol chloride and metoclopramide were administered in the first patient.

Once mechanical outlet obstruction has been ruled out, the usual treatment of postoperative atony is gastric aspiration and intravenous or jejunal feeding (Herman and Johnson, 1970). Recovery is spontaneous according to Kraft et al. (1964), who also claim that autonomic drugs have no effect. However, in some exceptional cases, mechanical decompression is insufficient to return the tonus of the gastric muscle to the level necessary for renewing gastric emptying. Contrary to the statement of Kraft et al. (1964), medical treatment may be beneficial. Bethanechol chloride has been successfully used (Bergin and Jordan, 1959; Sheiner and Catchpole, 1976). Metoclopramide has also been found to have some favourable effect in moderate cases (Stadaas and Aune, 1972; Sheiner and Catchpole, 1976). Carbachol has also proved to be effective in accelerating gastric emptying (Tinker et al., 1970). However, in our first case not only metoclopramide but also bethanechol chloride was unsuccessful and the patient remained in complete atony for 4 months. The unresponsiveness to these drugs may have been caused by the long delay between the operation and the onset of parasympathomimetic drug therapy.

Oxytocin is known to have a stimulant effect on the smooth muscle of the uterus and mammary gland. Goodman and Gilman (1975) state that its function, if any, in males is not known. When given for the induction of labour, no major effect on the gastrointestinal tract is observed. This probably results from the very small dosage necessary to obtain contraction of the gravid uterus. Moreover, it is possible that this is also due to the fact that in the gynaecological cases in which oxytocin is used the innervation of the gastrointestinal tract is presumably normal. Indeed, as Cannon (1939) has postulated in his 'law of denervation supersensitivity', it seems that denervation makes smooth muscle more susceptible to drugs. This has also been proved by Tinker et al. (1970), who found that subthreshold doses of carbachol provoke a significant acceleration of gastric emptying in vagotomized humans. Thus, although oxytocin has no effect on the intestines in induction of labour, it may be effective on the vagotomized stomach and this was the rationale of its use.

References

BERGIN W. F. and JORDAN P. H. (1959) Gastric atonia and delayed gastric emptying after vagotomy for obstructing ulcer. *Am. J. Surg.* **98**, 612–616.

CANNON W. B. (1939) A law of denervation. *Am. J. Med. Sci.* **198**, 737–750.

DONOVAN I. and ALEXANDER-WILLIAMS J. (1976) Postoperative gastric retention and delayed gastric emptying. *Surg. Clin. North Am.* **56**, 1413–1419.

DRAGSTEDT L. R., HARPER P. V., TOVEE E. B. et al. (1947) Section of the vagus nerves to the stomach in the treatment of peptic ulcer. *Ann. Surg.* **126**, 687–699.

EDWARDS D. A. W. and ROWLANDS E. N. (1968) Physiology of the gastroduodenal junction. In: CODE C. F. (ed.) *Handbook of Physiology*. Washington, DC, American Physiological Society, pp. 1985–2000.

GOODMAN L. S. and GILMAN A. (1975) *The Pharmacological Basis of Therapeutics*, 5th ed. New York, Macmillan, pp. 868–870.

HERMAN G. and JOHNSON V. (1970) Management of prolonged gastric retention after vagotomy and drainage. *Surg. Gynecol. Obstet.* **130**, 1044–1048.

KRAFT R. O., FRY W. J. and DE WEESE M. D. (1964) Postvagotomy gastric atony. *Arch. Surg.* **88**, 865–871.

NELSEN T. S., EIGENBRODT E. H., KEOSHIAN L. A. et al. (1967) Alterations in muscular and electrical activity of the stomach following vagotomy. *Arch. Surg.* **94**, 821–835.

SHEINER H. J. and CATCHPOLE B. N. (1976) Drug therapy for post-vagotomy gastric stasis. *Br. J. Surg.* **63**, 608–611.

STADAAS J. O. and AUNE S. (1972) Clinical trial of metoclopramide on post-vagotomy gastric stasis. *Arch. Surg.* **104**, 684–686.

TINKER J., KOCAK N., JONES T. et al. (1970) Supersensitivity and gastric emptying after vagotomy. *Gut* **11**, 502–505.

VASCONEZ L. O., ADAMS J. T. and WOODWARD E. R. (1970) Treatment of reluctant post-vagotomy stoma with bethanechol. *Arch. Surg.* **100**, 693–694.

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Autoparathyroidectomy: a case report

G. R. MCLATCHIE, E. W. MORRIS, A. FORRESTER AND I. FOGELMAN*

SUMMARY

This report describes a patient with primary hyperparathyroidism who became spontaneously normocalcaemic preoperatively. This was due to infarction in a parathyroid adenoma. Plasma parathormone (PTH) levels were monitored pre- and postoperatively.

SPONTANEOUS infarction of parathyroid adenomas resulting in a fall of serum calcium levels into the normal range is rare. It was first described by Norris (1946), but this is the first case report which includes details of the serum PTH levels.

Case report

A 51-year-old male presented to Glasgow Royal Infirmary with a 6-year history of increasingly frequent attacks of renal colic. In June 1976 an intravenous pyelogram (IVP) demonstrated a left hydronephrosis with ureteric dilatation to the 4th lumbar vertebra and a right renal pelvic calculus. After a left ureterolithotomy in late September 1976, the patient was noted to have repeatedly high fasting serum calcium levels with a low serum phosphate (*Table I*). Blood urea, plasma proteins and serum alkaline phosphatase were normal but plasma PTH was elevated to 1150 ng/l (normal range 500 ng/l). Iliac crest biopsy was histologically consistent with hyperparathyroidism. IVP demonstrated a large staghorn calculus in the right renal pelvis. The skeletal survey was normal.

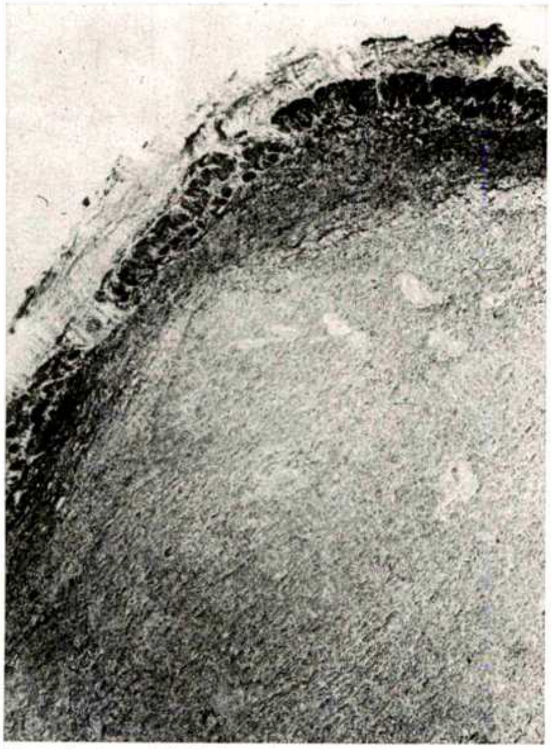

Fig. 1. Section of the infarcted parathyroid adenoma at low power showing an eosinophilic central area with peripheral normal glandular tissue. (×4.)

Table I: THE CHANGES IN SERUM CALCIUM, PHOSPHATE AND PARATHORMONE LEVELS BEFORE AND AFTER NECK EXPLORATION

Date	Calcium (mmol/l) (Normal = 2·2–2·6)	Phosphate (mmol/l) (Normal = 0·8–1·4)	Parathormone (ng/l) (Normal = <550 ng/l)
17.9.76	3·07	0·67	
15.10.76	3·42	0·52	
22.10.76	3·40	0·61	1150
9.1.77	2·30	0·95	
11.1.77	2·50	0·90	<190
20.1.77	Neck exploration		
21.1.77	2·15	0·65	
22.1.77	1·85	0·85	
24.1.77	2·05	0·80	
25.1.77	2·20	1·15	
26.1.77	2·15	1·10	<190
31.1.77	2·15	0·85	

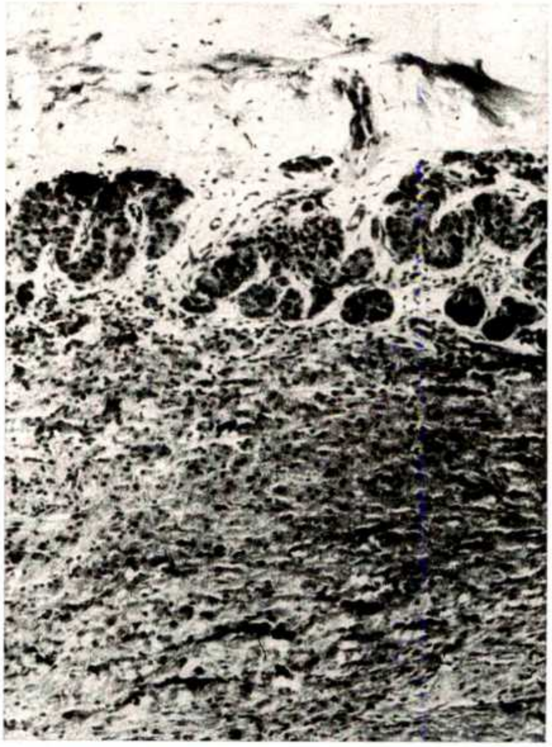

Fig. 2. Histological section of the infarcted adenoma at high power. Note that the peripheral rim consists of surviving glandular epithelium. The centre of the adenoma is replaced by necrotic tissue with ghost outlines of cells and blood vessels and is separated from the surviving normal parathyroid tissue by a layer of vascular fibrous tissue containing much stainable iron (*see also Fig.* 1). (×10.)

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Serum calcium and PTH levels returned to normal immediately prior to neck exploration but these results were not available to us until during the postoperative period. Three suspicious enlarged parathyroid glands were removed at operation. The patient recovered uneventfully. To date PTH and serum calcium levels have remained normal.

Pathological findings

Histologically the 2-cm mass removed from the region of the left upper pole of the thyroid was an infarcted chief cell adenoma with appearances suggesting infarction of some weeks' duration (*Figs.* 1 and 2). The two other glands were histologically normal.

Discussion

Spontaneous infarction of parathyroid adenomas in hyperparathyroidism, producing normocalcaemia, is rare. Previous cases have been reported by Connor et al. (1965), Johnston and Schnute (1961), Norris (1946) and Northcutt et al. (1969) but in none of these cases was serum PTH monitored.

The fall of serum calcium following spontaneous infarction varies in severity from acute tetany to fatal hypocalcaemia (Dowlatabadi, 1959). Neck pain has also been reported as an accompaniment to infarction (Howard et al., 1953). The case we describe had none of these features preoperatively. This may be explained by the fact that he had been on 2 μg of 1-alpha-hydroxy-vitamin D_3 for the 10 days prior to his neck exploration and this could account for the unusual finding of normocalcaemia only 4 days after exploration and after the removal of two normal parathyroid glands (Boyle et al., 1977).

It is thought that those cases of apparent cure in which adenomas, though present, have not been found at neck exploration, are due to compromise of the blood supply of the parathyroid glands (McGeown and Morrison, 1959).

Acknowledgements

The authors wish to thank Mr I. McLennan, Mr J. S. F. Hutchison, Dr Ian Boyle and Professor R. Goudie for their assistance in the preparation of this case report. We would like to express our gratitude to Miss B. Maguire for secretarial help in the preparation of the manuscript.

References

BOYLE I. T., FOGELMAN I., BOYCE B. et al. (1977) 1-Alpha-hydroxy-vitamin D_3 in primary hyperparathyroidism. *Clin. Endocrinol.* **7**, 215s–222s.

CONNOR T. B., CLARK J. W., MARTIN L. G. et al. (1965) Intermittent hyperparathyroidism. *Trans. Am. Clin. Climatol. Assoc.* **77**, 80–95.

DOWLATABADI H. (1959) Acute fatal parathyroid poisoning associated with necrosis of the parathyroid adenoma prior to death. *J. Clin. Endocrinol.* **19**, 1481.

HOWARD J. E., FOLLIS R. H., YENDT E. R. et al. (1953) Hyperparathyroidism. *J. Clin. Endocrinol.* **13**, 997–1008.

JOHNSTON C. C. and SCHNUTE R. B. (1961) A case of primary hyperparathyroidism with spontaneous remission. *J. Clin. Endocrinol.* **21**, 196–200.

MCGEOWN M. G. and MORRISON E. (1959) Hyperparathyroidism. *Postgrad. Med. J.* **35**, 330–335.

NORRIS E. H. (1946) Primary hyperparathyroidism. *Arch. Pathol.* **42**, 261–273.

NORTHCUTT R. C., LEVINSON J. D. and ERNEST J. B. (1969) Hypocalcaemia resulting from infarction of a parathyroid adenoma. *Ann. Intern. Med.* **70**, 353–356.

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Vascular Surgical Society of Great Britain and Ireland: Preliminary Notice

The Annual Meeting for 1979 is to be held in the newly opened John Radcliffe Hospital, Headington, Oxford, on Tuesday 18 December 1979. Overnight accommodation will be available before and after the meeting in Keble College where the Annual Dinner will be held. Transport by coach between Keble College and the John Radcliffe Hospital will be provided. The train service to Oxford is good and, if possible, should be used to avoid difficulties with car parking. Overnight luggage may be left in Keble College during Wednesday morning by Members staying on for Christmas shopping in the very fine bookshops nearby.

The local Secretary is Mr Howard Steer (Nuffield Department of Surgery, John Radcliffe Hospital, Headington, Oxford) who will circulate all members within the next few weeks giving further details of the meeting together with abstracts forms for those members wishing to offer papers; a 200 word summary will be required and the closing date for receiving this will be 10 October.

Br. J. Surg. Vol. 66 (1979) 554–557

Tracheal collapse after thyroidectomy

W. E. R. GREEN, H. W. H. SHEPPERD, H. M. STEVENSON AND W. WILSON*

SUMMARY

Tracheal collapse after thyroidectomy is uncommon; when it occurs, complete airway obstruction is often sudden, unexpected and fatal.

In this paper a patient treated for tracheal collapse by tracheostomy and followed up for 1 year is described and, from a review of the literature, a further 9 cases are presented. The aetiology of the condition, the patient at risk and the technique of management are discussed.

SOME cases of acute respiratory distress occurring after thyroidectomy for benign disease have been attributed to collapse of the trachea. Softening of the rings and loss of support from the surrounding goitre have been proposed as the causes of sudden and unexpected airway obstruction (Henry, 1927) which may prove fatal (Cooke, 1966). Normal vocal cord movement, the absence of glottic or subglottic oedema and exclusion of haematoma make a diagnosis of tracheal collapse likely if respiratory difficulty is encountered during or shortly after operation (Henry, 1927; Peterson and Rovenstine, 1936; Mayer, 1951), or up to 24 h later when the patient has returned to the ward (Marangos, 1951; Cooke, 1966). It occurs after removal of a long standing, toxic and often intrathoracic goitre, though cases have been reported in which the gland was neither large (Henry, 1927) nor toxic (Mayer, 1951). The condition is uncommon, there being 3 cases in a series of 600 thyroidectomies described by Henry (1927) and only 1 in a larger series of 1000 (Peterson and Rovenstine, 1936), and although recognized as a definite clinical entity (Joll, 1932) it has received only brief mention in some reviews (Plested and Pollock, 1967; Black, 1972; Beaugie, 1975) and none in others (Montgomery and Welbourn, 1963; Wade, 1965; Freeman, 1970; Martis and Athanassiades, 1971; Barraclough and Reeve, 1975). There have been reports of successful restoration of the airway by endotracheal intubation or tracheostomy (Henry, 1927; Joll, 1932) and also cases where the patient died despite intubation (Peterson and Rovenstine, 1936; Marangos, 1951) or because the airway obstruction was recognized too late (Cooke, 1966). The longer term management of this condition, and the prognosis if successfully treated, have not been reported in detail.

Case report

A 36-year-old man with a 3-year history of thyrotoxicosis presented initially with weight loss, muscle weakness, irritability and a moderate goitre. Treatment with neomercazole 15 mg b.d., thyroxine 0·2 mg b.d. and propranolol 40 mg q.i.d. rapidly controlled his symptoms and he became stable on maintenance therapy of neomercazole 15 mg/day and thyroxine 0·2 mg/day. He was referred for surgical treatment because of the continued presence of a goitre, although this was not causing pressure symptoms. Examination revealed a healthy, well-built man with a mild degree of pectus excavatum. There was a smooth goitre of moderate size in the neck with an associated bruit but no evidence of thyrotoxicosis. The respiratory system was normal. A chest X-ray showed no evidence of intrathoracic extension of the goitre. Routine haematological and biochemical investigations were normal.

At operation (W. W.) a five-sixths subtotal thyroidectomy was performed removing 180 g from a moderately vascular goitre. The remnant of each lobe was sutured to the fascia on either side of the trachea, which was not noticeably abnormal. Recovery from anaesthesia was uneventful and the patient was extubated. Complete airway obstruction occurred immediately and the patient was reintubated without difficulty, at which time both vocal cords were seen to move normally. A second attempt at extubation failed and a tracheostomy was therefore performed. Again the trachea was not obviously abnormal, and there was no difficulty in inserting a 39 Portex cuffed tracheostomy tube; there was no evidence of local oedema or haemorrhage.

A satisfactory airway was maintained after tracheostomy, but on the first postoperative day signs of hypocalcaemia were observed (serum calcium 1·81 mmol/l) and the patient required calcium supplements for a further 7 days. Tomograms of the upper air passages showed considerable subglottic narrowing of the trachea (*Fig.* 1) but this narrowed segment expanded well during a Valsalva manoeuvre. X-rays were taken with the tracheostomy tube removed and the patient was able to breathe, although with very considerable inspiratory stridor. On the fourth postoperative day the Portex tracheostomy tube was changed to a size 28 Silver tube and the day after a further change was made to a 26 with a speaking valve.

The patient was unable to tolerate blocking of the tube at night, particularly when lying flat, but during the day a satisfactory airway was maintained. On the eighteenth postoperative day a bronchoscopy (H. M. S./W. E. R. G.) was performed; the vocal cords were normal and the trachea had an adequate lumen. The patient recovered quickly from anaesthesia and was able to maintain a satisfactory airway. The tracheostomy tube was not replaced. Some respiratory difficulty was again noted at night, particularly with the clearing of secretions; sleeping well propped up was found to be most comfortable. Over the next 2 days stridor during a normal respiratory effort disappeared, and the patient's voice, which had been moderately hoarse after extubation, improved.

A laryngoscopy (H. W. H. S.) was performed on the twenty-second postoperative day, which showed normal cord movement but still some narrowing of the trachea, which appeared as an anterior/posterior slit tending to collapse inwards during inspiration. The patient continued to improve and one month after operation the tracheostomy wound had closed, there was minimal inspiratory stridor on exertion, he was able to cough and clear secretions and to sleep lying flat without distress.

Follow-up at 1 year has revealed a satisfactory outcome; the patient remains euthyroid, with a normal voice and no respiratory distress either at rest or during exertion. Further radiographs of the larynx and trachea have revealed some degree of subglottic narrowing (*Fig.* 2) which appeared to be at the level of the original collapse; on tracheoscopy, however (H. W. H. S.), a stricture at the level of the original tracheostomy was found and the distal trachea was normal.

Discussion

Aetiology

It has been suggested that a firm goitre of long standing, crowding the trachea, may lead to loss of elasticity and even disappearance of the rings (Henry, 1927); removal of the surrounding gland may then

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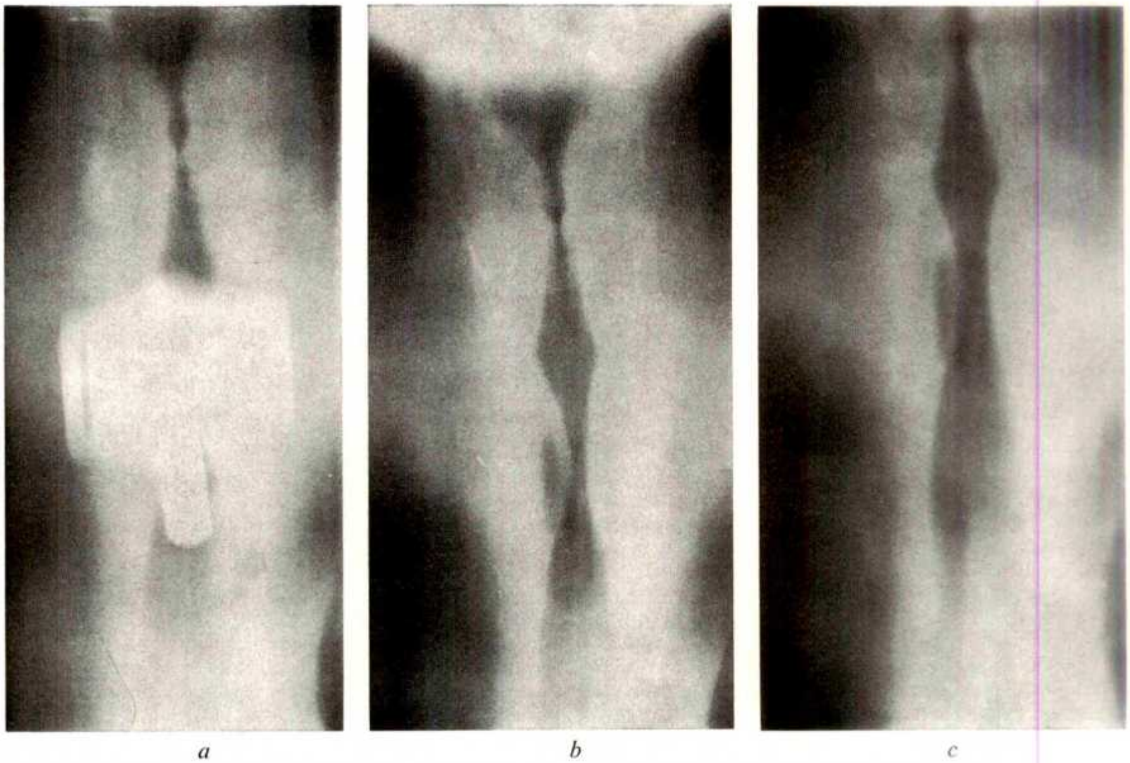

Fig. 1. Tomograms of the larynx and trachea. *a*, Position of the tracheostomy tube. *b*, With the tube removed showing the partially collapsed trachea. *c*, Dilatation of the trachea during a Valsalva manoeuvre.

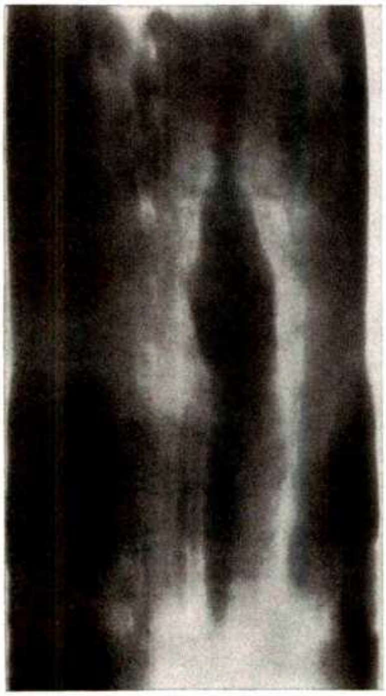

Fig. 2. Tomogram of the larynx and trachea 1 year after surgery showing minimal narrowing and deformity of the trachea.

result in collapse of the unsupported airway. Displacement or deformation of the trachea, without softening, is unlikely to result in airway obstruction (Henry, 1927) since the natural resilience of the rings will permit it to spring open (Lahey and Hoover, 1951). An alternative hypothesis of tracheal spasm was investigated experimentally in the dog by Cole (1939), prompted by his own experience of serious stridor in a patient undergoing thyroidectomy. He concluded that although spasm of the trachealis muscle could produce some narrowing of the normal trachea it did not induce collapse, and a negative airway pressure of −70 mmHg also failed to narrow the lumen by any greater amount than that produced by muscle spasm. It was felt that although respiratory difficulty and stridor might at times be associated with mechanical changes in the configuration of the lumen, collapse of the walls with complete obstruction was unlikely to occur unless the trachea was pathologically soft.

The patient at risk

The condition, despite the uncertainty as to its cause, has been recognized for many years (Joll, 1932; Marangos, 1951; Cooke, 1966), although the patient at risk, generally assumed to be the treated thyrotoxic case, has not been clearly defined. In this review of the reported cases (*Table I*) it was found that although more of the patients had at some time been thyrotoxic, the condition did not occur exclusively in this group nor was the size or position of the goitre of predictive value; all the patients appeared to have had thyroid dysfunction for more than a year but information on

Table I: TRACHEAL COLLAPSE: DETAILS OF 9 CASES

Series	Goitre	Toxic	Recognized at op.	Treatment	Result	Time of death
Henry (1927)	Moderate	Yes	Yes	Endotracheal tube	Alive	—
	Moderate	Yes	No	Endotracheal tube	Alive	—
Joll (1932)	Moderate	Yes	No	Tracheostomy	Alive	—
Peterson and Rovenstine (1930)	Large	Yes	Yes	Endotracheal tube	Died	6 h
Mayer (1951)	Large	No	Yes	Endotracheal tube	Alive	—
Marangos (1951)	Small	No	No	None	Died	12 h
	Large intrathoracic	No	No	Tracheostomy	Died	3 h
	Moderate	No	Yes	Tracheostomy	Alive	—
Cooke (1966)	Moderate	Yes	Yes	None	Died	24 h

the exact length of time for which a goitre had been present was not available. Marangos (1951) has emphasized the need to examine the trachea at operation for evidence of softening, but in many patients, including our own, this has not proved helpful in anticipating subsequent airway obstruction due to collapse.

The crisis may occur during the operation if the procedure is performed without endotracheal anaesthesia (Henry, 1927; Peterson and Rovenstine, 1936; Mayer, 1951) or during the recovery period as respiratory effort increases, sometimes up to 24 h after operation (Marangos, 1951; Cooke, 1966). Symptoms of respiratory difficulty usually appear suddenly, without warning, and progress rapidly to complete airway obstruction. In the cases reviewed there was a mortality of 44 per cent.

Management

There has been no clear guidance on the management of this condition. If recognized at operation, suturing of the trachea to the soft tissues of the neck has been advocated (Henry, 1927; Joll, 1932; Peterson and Rovenstine, 1936) although it is difficult to believe that this manoeuvre would be sufficient to hold the airway open against the negative pressure of inspiration, and in the one case reported in which this was done the patient subsequently required tracheostomy when the trachea collapsed and became obstructed 12 h after operation (Marangos, 1951).

Intubation has been employed for as long as 24 h (Henry, 1927) and as little as 3 h (Mayer, 1951). Peterson and Rovenstine (1936) have stressed that a trachea which has collapsed is likely to do so again, citing a patient, extubated after only 6 h, who died a short while later of asphyxia due to sudden reobstruction of the airway. In a general review of airway obstruction associated with thyroid disease, Lahey and Hoover (1951) stressed that mediastinitis was not a problem if tracheostomy had to be performed in association with thyroid surgery.

The sudden complete airway obstruction requires urgent relief and, although temporary respite may be gained for the patient by face-mask ventilation or mouth-to-mouth rescuscitation, a definitive procedure must be performed without delay.

Coniotomy (Oppenheimer, 1974) and needle tracheostomy (Lee, 1978) are both inappropriate in this situation as the entry point into the trachea is certain to be above the part which has collapsed; the choice therefore lies between endotracheal intubation and tracheostomy. The use of PVC tubes and low pressure 'floppy' cuffs has greatly diminished the risk of tracheal injury after prolonged intubation by either route (Cooper and Grillo, 1972; Crawley and Cross, 1975) and stenosis is most likely to occur at the site of the stoma after tracheostomy (Friman et al., 1976), particularly if this has been carelessly or incorrectly fashioned (Lulenski and Batsakis, 1975). In this situation, where the trachea is already abnormal and possibly distorted, endotracheal intubation, if possible, is to be preferred. On the other hand, time should not be wasted trying to perform a difficult intubation when reopening of the wound will expose a trachea already bare of veins and thyroid tissue. The final choice must depend very much on the time and place at which the crisis occurs and the skill of the clinician at hand.

Intubation is required for at least 24 h, and if tracheostomy has been performed the softened airway, further weakened by the creation of a stoma, may require splinting for a considerably longer period. Patients managed with an endotracheal tube can probably be extubated after 24–48 h provided that facilities are available for its replacement, if necessary. Patients with a tracheostomy may be treated either by progressive reduction in the size of the tube, as in our own case, or by trial removal of the tube at 5 days. In our own experience although some lateral movement of the tracheal wall may be seen and clinical stridor persist for some days, neither is an indication to prolong intubation.

Longer follow-up of our own case has confirmed that tracheostomy is not without risk to the integrity of the airway, although the radiological and endoscopic findings do not correlate with the clinical condition of the patient.

Conclusion

From this review it appears that collapse of the trachea, although uncommon, may occur in any patient undergoing thyroidectomy; the individual at risk does not appear to be determined by the nature of the thyroid disorder, nor by the size or position of the goitre. Respiratory difficulty may present unexpectedly at any time during the first 24 h after operation and is likely to prove fatal unless treated immediately.

Immediate restoration of the airway is essential, after which the diagnosis can usually be made by exclusion of cord paralysis, oedema and haematoma. The airway should be maintained by intubation for a minimum of 24 h and for a more prolonged period if respiratory distress continues.

The choice between endotracheal intubation and tracheostomy is more likely to be determined by the skill of the clinician on hand at the time of the crisis although endotracheal intubation may be preferable to tracheostomy if subsequent stenosis of the trachea is to be avoided.

References

BARRACLOUGH B. H. and REEVE T. S. (1975) Postoperative complications of thyroidectomy. A comparison. *Aust. NZ J. Surg.* **45**, 21–29.

BEAUGIE J. M. (1975) *Principles of Thyroid Surgery*. Tunbridge Wells, Pitman Medical, p. 210.

BLACK B. M. (1972) Surgery for Graves' disease. *Mayo Clin. Proc.* **47**, 966–968.

COLE W. H. (1939) Laryngeal spasm and so-called tracheal collapse. Experimental and clinical studies. *Arch. Surg.* **39**, 10–27.

COOKE R. V. (1966) Thyroid disease and thyroidectomy. *Ann. R. Coll. Surg. Engl.* **39**, 201–212.

COOPER J. D. and GRILLO H. C. (1972) Analysis of problems related to cuffs on intratracheal tubes. *Chest* **62**, 21S.

CRAWLEY B. E. and CROSS D. E. (1975) Tracheal cuffs. A review and dynamic pressure study. *Anaesthesia* **30**, 4–11.

FREEMAN C. G. (1970) Complications of thyroid surgery. *Surg. Clin. North Am.* **70**, 409–425.

FRIMAN L., HEDENSTIERNA G. and SCHILDT B. (1976) Stenosis following tracheostomy. A quantitative study of long term results. *Anaesthesia* **31**, 479–493.

HENRY C. K. P. (1927) Tracheal collapse during thyroidectomy. *Current Res. Anesth. Analg.* **6**, 146–148.

JOLL C. A. (1932) *Diseases of the Thyroid Gland*. London, Heinemann, p. 578.

LAHEY F. H. and HOOVER W. B. (1951) Tracheotomy after thyroidectomy. *Ann. Surg.* **133**, 65–76.

LEE T. H. (1978) Needle tracheostomy for acute upper airway obstruction. *Br. Med. J.* **1**, 281–282.

LULENSKI G. C. and BATSAKIS J. G. (1975) Tracheal incision as a contributing factor to tracheal stenosis. Experimental study. *Ann. Otol. Rhinol. Laryngol.* **84**, 781–786.

MARANGOS G. (1951) Tracheostomy after thyroidectomy. *Ann. Surg.* **134**, 927–928.

MARTIS C. and ATHANASSIADES S. (1971) Post-thyroidectomy laryngeal edema. *Am. J. Surg.* **122**, 58–60.

MAYER E. C. JUN. (1951) Tracheal collapse during thyroidectomy. *Current Res. Anesth. Analg.* **30**, 238–239.

MONTGOMERY D. A. D. and WELBOURN R. B. (1963) *Clinical Endocrinology for Surgeons*. London, Arnold.

OPPENHEIMER R. P. (1974) Airway. Instantly. *JAMA* **230**, 76.

PETERSON M. C. and ROVENSTINE E. A. (1936) Tracheal collapse complicating thyroidectomy. Case report. *Curr. Res. Anesth. Analg.* **15**, 300.

PLESTED W. G. and POLLOCK W. R. (1967) Hyperthyroidism. *Arch. Surg.* **94**, 517–523.

WADE J. S. H. (1965) Three major complications of thyroid surgery. *Br. J. Surg.* **52**, 727–731.

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Statistics in *The British Journal of Surgery*

It is part of the clinical scientist's stock-in-trade to use statistical methods. In many instances, and by most readers, these can be taken on trust, but in that there is a wide variety of tests and, on occasion, disagreement amongst both amateurs and professionals on the best choice, it is always wise that authors quote the method used. It is indeed journal policy to quote methods, the reason for their choice and, in the case of clinical trials, the confidence or tolerance limits of the observed results. Delay in acceptance may occur if contributors do not include these details.

Br. J. Surg. Vol. 66 (1979) 558–561

Carcinoma of the thyroid

T. T. ALAGARATNAM AND G. B. ONG*

SUMMARY

Total thyroidectomy with excision of any enlarged cervical lymph nodes was the usual operation practised for carcinoma of the thyroid in this series. Extended thyroidectomy afforded cures in some patients with locally advanced disease. Preoperative drill biopsy of the goitre was a useful procedure. Other noteworthy features were the increasing occurrence of papillary carcinoma and the comparatively high incidence of malignancy in solitary nodules.

CARCINOMA of the thyroid is an uncommon tumour which accounts for 0·7 per cent of all cancers in women and 0·2 per cent in men (Waterhouse, 1974). Patients in the present review were all admitted to the University Surgical Unit at the Queen Mary Hospital, Hong Kong. The unit deals with all types of surgical case, so that the patients were in no way selected. They were operated on by surgeons of varying experience from registrars to consultants. Goitre has not been an endemic illness in Hong Kong and the present review is of a population in which goitre is no more frequent than other major illnesses.

From 1964 to 1976 there were 124 cases all of which were histologically proved to be malignant. The classification recommended by the WHO was used; the histology of earlier patients was reviewed and reclassified. Twelve patients who were lost to follow-up were excluded.

Patients and methods

Incidence

Over the 13 years there has been a gradual increase in the incidence of thyroid carcinoma (*Table I*). In 1964, there were 9 cases of carcinoma: follicular carcinoma comprised 55 per cent and papillary carcinoma, 11 per cent. A third of the 9 cases were in the 41–50 age group. In 1976, there were 26 cases of carcinoma, and the increase was mostly in the 21–30 age group. Papillary carcinoma (39 per cent) showed a striking increase (almost fourfold), whilst the incidence of follicular carcinoma was slightly diminished (43 per cent). During this period 751 cases of benign goitre underwent surgery, giving an overall operative incidence of 16 per cent for carcinoma.

The incidence in terms of age and the proportion of males in the series is shown in *Figs*. 1 and 2 respectively. Follicular carcinoma shows two 'peaks', one in the younger (20–30) and the other in the older (50–60) age group. In the latter group, anaplastic carcinoma was also frequent. In the elderly male patients follicular carcinoma and anaplastic carcinoma were most frequently encountered; in younger men papillary carcinoma was more frequent. The overall incidence in males was 21 per cent. There were no cases of carcinoma in children in the present series.

Follicular carcinoma was the most common, followed closely by the papillary variety (*Table II*). There were 13 cases of anaplastic carcinoma and 3 cases of medullary carcinoma. Malignant lymphoma was a rare lesion. Two cases of laryngeal carcinoma presented clinically as a thyroid swelling; and one patient with carcinoma of the breast developed a metastatic nodule in the thyroid. These 3 cases have been excluded from the series.

Mode of presentation: A clinical diagnosis of thyroid carcinoma was possible in 17 per cent of the series. Unmistakable features of carcinoma such as a recent rapidly enlarging goitre with

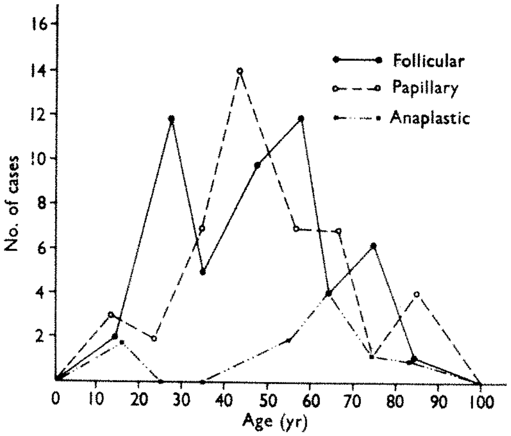

Fig. 1. Distribution by age of carcinoma of the thyroid.

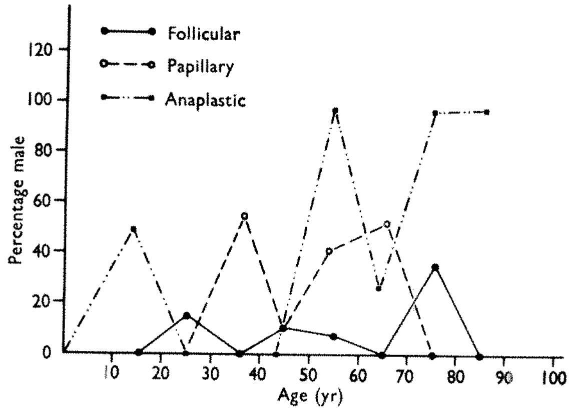

Fig. 2. Male incidence of carcinoma of the thyroid.

Table I: INCIDENCE OF CARCINOMA OF THE THYROID OVER A 13-YEAR PERIOD

Period	No. of cases
1964	9
1965–7	21
1968–70	18
1971–3	27
1974–6	49

Table II: DISTRIBUTION OF PRIMARY CARCINOMA OF THE THYROID

Follicular	50
Papillary	45
Anaplastic	13
Medullary	3
Malignant lymphoma	1

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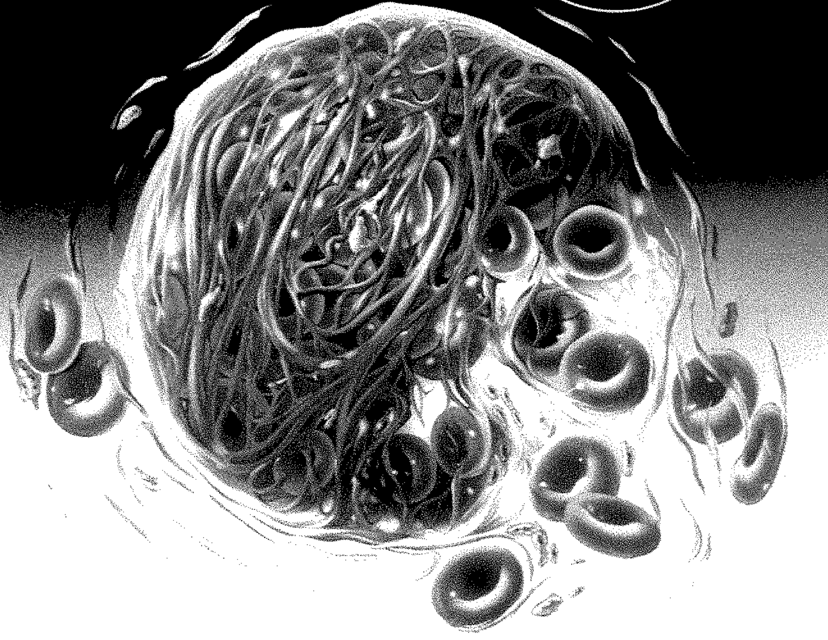

The first tissue-culture urokinase for the treatment of pulmonary embolism.

With significant advantages, both clinical and practical, over other thrombolytics, anticoagulant therapy and surgery.

- **Abbokinase achieves rapid clot lysis by a direct action on the fibrinolytic mechanism. Urokinase has a greater affinity for plasminogen within the formed clot (gel phase plasminogen) than for circulating plasminogen (sol phase plasminogen)[1] and is therefore the most selective thrombolytic agent in current use.[2]**
- **Abbokinase is devoid of antigenic activity in humans – unlike streptokinase. This obviates prior antibody testing and the need for corticosteroids for the prevention and alleviation of allergic response.[3]**
- **Abbokinase is more successful than anticoagulants which do not lyse the clot or reopen the vessel.[4,5]**
- **Abbokinase is more economical and less traumatic than surgery.**

Data sheet information: **Presentation** Abbokinase is available in 10ml vials containing 250,000iu of a highly purified sterile lyophilised formulation of urokinase obtained from cultures of human kidney cells. Urokinase is a plasminogen activator excreted in the urine of normal healthy individuals. When reconstituted with 5.2ml distilled water according to directions, each ml of isotonic solution will contain 50,000iu urokinase, 5mg mannitol and 9mg sodium chloride. **Uses** Abbokinase in vivo and in vitro produces the release of plasmin by an enzymatic action on human plasminogen. Abbokinase has only minimal activity in reducing fibrinogen levels but blood plasminogen levels are reduced, the effect being dose-dependent. Abbokinase is virtually non-antigenic to humans and, in therapeutic doses, is thromboplastin-free. Thrombolytic therapy is indicated in the treatment of vascular occlusions caused by forming or recently formed fibrin clots. Theoretically the best results will be obtained with thrombi less than 24 hours old. Abbokinase is indicated as a thrombolytic agent in pulmonary embolism. **Dosage and Administration** Abbokinase is administered intravenously by continuous infusion, usually for a period of 12 hours. It is recommended that Abbokinase be given in a solution of Normal Saline by constant infusion. An initial loading dose to be given during the first ten minutes of therapy is advocated. This loading dose should be equal to the amount which it is planned to administer over each succeeding period of one hour. Ideally an infusion pump should be used to maintain a constant rate of infusion. Abbokinase is reconstituted with 5.2ml sterile water for injection, without preservatives. For administration the reconstituted solution should be further diluted with normal saline to the total volume of solution (195ml) for a 12 hour treatment including the priming dose. From this solution, 15ml are given over a period of 10 minutes as the priming dose and the remainder over a period of 12 hours at the rate of 15ml/hour. Dosage: It should be noted that patient-to-patient variation in response can be expected, due to individual variation in levels on inhibitory factors. Certain disease states such as uraemia, some malignancies and dyslipidaemias can be associated with an increased plasma level of urokinase or plasmin inhibitors. In other conditions such as massive pulmonary embolism, endogenous fibrinolytic activity may be increased. The recommended dosage regimen for the treatment of pulmonary embolism is: Loading dose: 4,400iu per kg bodyweight over 10 minutes. Constant infusion dose: 4,400iu per kg bodyweight per hour. Duration of infusion: 12 hours. **Contra-indications, Warnings, etc.** Contra-indications: Manifest or recent (i.e. within 3 days) haemorrhage. Any haemorrhagic diathesis. Severe hypertension. During cardiopulmonary resuscitation. During pregnancy or suspected pregnancy. Warnings and Precautions: The major adverse effect of Abbokinase is haemorrhage, usually associated with too high dosage. A high incidence of bleeding from minor skin lesions, therapeutic and diagnostic puncture sites and pre-existing gastro-intestinal lesions has been observed with high dosages. Any evidence of significant internal bleeding necessitates the cessation of thrombolytic therapy. An anti-fibrinolytic agent such as epsilonaminocaproic acid (EACA) may be used as an antidote if required. Epsilonaminocaproic acid should be available for use, if necessary, during infusions with Abbokinase when high doses are being administered. Post-partum for one month. Recent surgery (within 3 days). Concurrent anti-coagulant therapy should be administered cautiously. Mild temperature increases have been observed during thrombolytic therapy with Abbokinase. When there is a history of hypersensitivity to drugs etc., caution is advised and facilities as well as corticosteroids, adrenaline, etc. should be readily available when Abbokinase is infused. Monitoring: The monitoring of fibrinolytic activity and of plasminogen levels is desirable. Pharmaceutical Precautions: The lyophilised powder should be stored at 2-8°C. Reconstituted solution should be used immediately after mixing and secondary dilution. **Legal Category** POM. **Package Quantities** Available in packs of 2 vials of 250,000iu each (List No. 6109). **Further Information** The potency of Abbokinase is expressed in International Units (iu). For practical purposes the iu is considered by most authorities to be equivalent to the CTA unit. The Ploug unit is usually considered to be equal to 1.4iu. **Product Licence Number** 0037/0096. **References** 1. Kakkar V.V, Scully M.F. Thrombolytic therapy *Brit. Med. Bull.* **34(2)**: 191–199, 1978. 2. Kakkar V.V, Scully M.F. *Op. cit.*, p.192. 3. Genton E, Claman H.N. Urokinase: antigenic studies in patients following thrombolytic therapy *J. Lab. Clin. Med.* **15**: 619, 1970. 4. Urokinase Pulmonary Embolism Trial: Phase I results: a cooperative study, *JAMA* **214**: 2163, 1970. 5. Urokinase Pulmonary Embolism Trial Study Group: Urokinase-streptokinase Embolism Trial *JAMA* **229**: 1606, 1974. Further information available on request from Abbott Laboratories Limited, Queenborough, Kent ME11 5EL. ® Registered Trade Mark of Abbott Laboratories Ltd. AK389

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hard areas, widespread skin and muscle involvement, or the presence of enlarged hard cervical lymph nodes simplified the diagnosis. In 2 patients the tumour had ulcerated. In a further 13 per cent malignancy was suspected at the initial clinical examination, though no overt clinical signs were present. In 70 per cent of patients, however, the presentation was that of a clinically benign goitre and malignancy was diagnosed on histology alone. The majority of thyroid carcinomas presented as solitary nodules, and, when compared with benign nodules seen over this period, the incidence of malignancy in solitary nodules was 25 per cent. Solitary nodules were present in all age groups, but were most frequent in the 30–50 group. Five patients in the present series had been treated for thyrotoxicosis. Four patients were treated with anti-thyroid drugs and one had undergone subtotal thyroidectomy. Twenty-three per cent of the cases presented with a multinodular goitre.

The type of goitre giving rise to carcinoma is shown in *Table III*. Follicular carcinoma was more common than the papillary variety in multinodular goitres and these usually presented in an older age group than solitary nodules; toxicity appeared to be more often associated with follicular than papillary carcinoma. Palpable cervical lymph nodes were present in only 2 cases of follicular carcinoma. In 8 cases of papillary carcinoma, clinically palpable (and histologically proved) lymph nodes were present. In another 11 cases, enlarged lymph nodes were found at operation, and of these 6 were free of tumour. In the majority of patients with papillary carcinoma the tumour was found to have breached the capsule of the thyroid gland and early infiltration to adjacent structures was observed. There were only 4 cases of occult papillary carcinoma. Early presentation was certainly not a feature in our patients. Only 20 per cent presented with a history of less than a year; the majority presented with a history of between 2 and 8 years with a median of 6 years. The commonest reason for seeking treatment was a gradual increase in the size of the goitre. In 10 per cent of the patients, however, the goitre had been present for 10–30 years with a median of 25 years. Recent rapid increase in size with symptoms relating to pressure on the trachea or oesophagus had eventually prompted presentation. In cases of anaplastic carcinoma the majority of patients presented with severe compression symptoms such as breathlessness, hoarseness, dysphagia and a persistent cough of short duration. In all types of carcinoma, the commonest compression symptom when present was dyspnoea, followed closely by hoarseness and dysphagia. Pain was an occasional symptom.

Drill biopsy: Since 1971 it has been our routine procedure to perform drill biopsy in all patients with thyroid lesions using a pneumatic drill fitted with a hollow needle. Over 400 patients have had this procedure performed with few complications (Ma et al., 1975). In the present series, drill biopsy was performed in 42 cases; in 25 patients (59·5 per cent) the biopsy was helpful in detecting malignancy of all histological types. Only 3 of the 42 patients had overtly malignant lesions. Preoperative biopsy was thus of great value in confirming malignancy in those who presented with goitres that clinically appeared to be benign. In particular drill biopsy enabled the surgeon to perform a planned total thyroidectomy for follicular carcinoma rather than a two-stage thyroidectomy necessitated by equivocal frozen sections of the tumour at the initial operation. Needless to say, such reoperation is hazardous, even for the most experienced surgeon. In 1971 there were 4 of a total of 6 patients who required such a two-stage total thyroidectomy. In 1976, with greater experience in interpreting histology from the small piece of tissue obtained by drill biopsy, 5 of a total of 12 patients required reoperation.

Treatment

Follicular carcinoma: All 50 cases of follicular carcinoma were treated by total thyroidectomy; in some, for reasons mentioned earlier, the operation was staged, the remaining lobe of the gland being excised 2–3 weeks after the initial operation. In 2 patients with advanced local disease, extended thyroidectomy was performed. One of the patients survived for 6 years and the other was lost to follow-up after 3 years.

Papillary carcinoma: Total thyroidectomy was performed in 25 cases, and hemithyroidectomy in 20. Nineteen patients had associated enlarged cervical lymph nodes which were excised. No formal radical block dissections of the neck were performed. Four patients who initially had hemithyroidectomy returned with tumour in the opposite lobe 6–10 years later. Extensive local recurrence after total thyroidectomy occurred in 1 patient and extended thyroidectomy afforded good palliation for 6 years.

Table III: TYPE OF GOITRE GIVING RISE TO CARCINOMA

	Follicular	Papillary	Anaplastic
Multinodular goitre	12	7	6
Solitary nodule	34	37	7
Associated with thyrotoxicosis	4	1	—

Table IV: SURVIVAL BY AGE

Age at presentation	Type of carcinoma	5-year survival (%)	10-year survival (%)
< 50 years	Papillary	75	40
	Follicular	66	30
> 50 years	Papillary	65	40
	Follicular	54	20

Anaplastic carcinoma: In this group total thyroidectomy was performed in 6 of the 13 patients; partial thyroidectomy was performed in 2 patients; in a further 2 patients, advanced local disease permitted only local resections around the trachea, without any form of thyroidectomy. All patients were given postoperative external irradiation. One patient presented with such advanced local disease that only external irradiation was possible. Extended thyroidectomy involving laryngectomy and partial excision of the oesophagus was performed in 2 patients; both patients, however, succumbed from leaks at the oesophageal suture line.

Medullary carcinoma: There were only 3 cases of medullary carcinoma and all were treated by total thyroidectomy. One case presented with a massive retrosternal extension requiring a combined cervical and total sternum-splitting incision.

Results

Operative mortality

There were 4 deaths. In addition to the 2 patients mentioned earlier who died from extended thyroidectomy for anaplastic carcinoma, one patient died from cachexia due to advanced disseminated disease which was not detected preoperatively. Uraemia due to coexisting chronic pyelonephritis was the cause of death in another patient.

Complications

Two of the major complications following total thyroidectomy are hypoparathyroidism and damage to the recurrent laryngeal nerves. In the present series there was a 9 per cent incidence of tetany, which frequently occurred following a planned total thyroidectomy rather than following a two-stage thyroidectomy for follicular carcinoma. The incidence of permanent recurrent laryngeal nerve damage was 2·6 per cent. There was no damage to the cervical sympathetic chain. Reoperation for evacuation of a haematoma was necessary in 2 cases.

Survival

The overall survival for papillary carcinoma was 70 per cent at 5 years and 40 per cent at 10 years. In follicular carcinoma it was 50 per cent and 25 per cent respectively. Patients with anaplastic carcinoma fared poorly—there was only 1 survivor at 5 years. Survival figures for male patients were definitely inferior; there were no 10-year survivals among the males. Younger patients (less than 50 years) fared better than older ones (*Table IV*).

Discussion

The increasing incidence of papillary carcinoma, particularly in younger patients, appears in most series. In his review Crile (1971) has commented on the almost doubled increase in papillary carcinoma occurring in a relatively younger age group. Similar increases have been noted by Beahrs et al. (1951), Campbell and Sage (1975) and Heitz et al. (1976). Explanations for such an increase are hard to find. None of our patients had any history of childhood irradiation to the head and neck, nor was any exposed to atomic irradiation. Doniach (1969) suggested than an increased intake of iodine could be a factor, but there is no evidence to suggest that this is so in our local population. An increasing awareness of thyroid carcinoma and refinements in the histological diagnosis of carcinoma by pathologists would perhaps be partly responsible for the increasing incidence of carcinoma; but its occurrence in a younger age group is at present inexplicable. In most series papillary carcinoma appeared to be the predominant cancer; whilst this is true in non-endemic areas, in an endemic area such as Cali, Colombia, Wahner et al. (1966) noted a predominance of follicular carcinoma. In the present series there is an even balance between the papillary and follicular forms. There were only 3 cases of medullary carcinoma and none of them were familial or associated with phaeochromocytoma.

The commonest mode of presentation was a solitary nodule. When compared with similar benign nodules, the incidence of malignancy was 25 per cent; this is much higher than that quoted in most series. The incidence of malignancy in multinodular goitre has been around 10 per cent (Cope et al., 1949, 10 per cent; Crile and Dempsey, 1949, 10·9 per cent). In the present series it was 9 per cent. Diagnosing malignancy preoperatively in a multinodular goitre has always been a difficult problem. It is slightly easier in a male patient with multinodular goitre in a non-endemic area; these should be viewed with great suspicion as thyroid carcinoma in males is more common than in females with goitre.

The dependence of thyroid carcinoma for its continued growth on thyrotrophic stimulating hormone has been firmly established by experimental and clinical observations. Surgical removal of the tumour followed by thyroxine therapy has now come to be accepted treatment. However, the extent of the operation has been a controversial question. Papillary carcinoma has been shown to be multifocal and the extent to which this has been observed to occur has depended on the thoroughness of examination of the gland removed at operation or at autopsy. Figures from 78 per cent (Clark et al., 1969) to 20 per cent (Block et al., 1960) have been reported. Total thyroidectomy would appear therefore to be the ideal treatment for papillary carcinoma. In the follicular variety, total thyroidectomy is essential to facilitate treatment of metastases by radioactive iodine; it also ensures removal of any tumour in the opposite lobe occurring as a result of intraglandular spread. The operation of total thyroidectomy, however, is not without its complications, permanent hypoparathyroidism being one of them (2 per cent reported by Thompson et al., 1973, to 33 per cent reported by Harold and Wright, 1966). Lesser operations have been performed, but these are not without their problems. McLintock (1968) has reported a 19 per cent recurrence after bilateral subtotal lobectomy; 13 per cent after lobectomy alone; and 6 per cent for lobectomy on the primary side and subtotal lobectomy on the contralateral side. Subtotal thyroidectomy with postoperative ablation of the remaining thyroid with radioactive iodine must always be a second-best procedure. Normal thyroid tissue would be certainly destroyed, but if tumour cells were present in the remaining thyroid tissue, then early recurrence is a probability as only 35 per cent of follicular carcinomas and 20 per cent of papillary carcinomas take up radioactive iodine (Scott, 1974). Another feature of papillary carcinoma which lends support to the idea of total thyroidectomy has been the late occurrence of a second carcinoma in patients who have had an initial lobectomy—Russell et al. (1969) recorded 4 per cent; Tollefson and De Cosse (1963), 3·7 per cent; Block et al. (1960), 7 per cent. Although these figures indicate an infrequent occurrence of a second carcinoma, the present writers agree with Hirabayashi and Lindsay (1961) that total thyroidectomy is still the best treatment for papillary carcinoma. This has been practised whenever a preoperative diagnosis (by drill biopsy) was possible. When, however, in an apparently 'benign' adenoma, the subsequent paraffin section revealed carcinoma, a second operation was not performed as the risk of inflicting permanent hypoparathyroidism was greater than the risk of a second carcinoma developing in the opposite lobe.

Taylor (1974) advocates total thyroidectomy only when the cervical lymph nodes are enlarged, believing that intraglandular spread to the opposite lobe occurred more frequently in such a situation. Four patients with papillary carcinoma who had unilateral lobectomy performed in the earlier years of the present series returned subsequently with tumours in the opposite lobe. In none of these patients was there any evidence of intraglandular spread at the initial operation. All 4 patients, however, had stopped taking thyroxine 1–2 years after surgery, and it is interesting to speculate whether recurrence would have occurred had they taken thyroxine regularly. In none of these patients was there any change in the histology from a well-differentiated form to a more anaplastic type.

In recent years, the trend in thyroid surgery has been away from radical or extended operations; few, if any, would perform standard radical block dissection of the neck or dissect the mediastinum for enlarged lymph nodes. Extended operations involving resection of the larynx, trachea or oesophagus are also infrequent, possibly because patients are now presenting for treatment at an earlier stage of the disease. Dajillian et al. (1974) recorded 6 survivors for periods varying from 5 months to 5½ years without evidence of local recurrence after total or partial laryngectomy as part of an extended operation. Although the morbidity and mortality are high, the present writers feel that there is still a place for such operations when the patient is first seen with extensive disease at an advanced stage in the neck, or with local recurrence. In the present series 2 of the 5 patients who underwent operation were able to live for 5 and 6 years respectively.

Patients with papillary carcinoma had a more favourable prognosis than those with follicular carcinoma. Other features such as male sex, age over 50 and extra-thyroid disease have been shown to be consistently associated with a poorer prognosis. These findings have been confirmed in this present series. The late presentation of many of our patients accounts for the slightly poorer survival values when compared with most Western series. One interesting feature which has been discussed in many large series is the effect of enlarged lymph nodes on prognosis. Some believe that the presence of metastatic cervical lymph nodes is associated with a better prognosis and a lesser mortality (Hirabayashi et al., 1961; Clark et al., 1967). Cady et al. (1976), in a review of four decades of thyroid surgery in the Lahey Clinic, have found evidence for this view. In the present study, however, there was no evidence to suggest that patients with tumour-bearing lymph nodes fared better than those without.

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References

BEAHRS O. H., PEMBERTON J. and BLACK B. M. (1951) Nodular goitre and malignant lesions of the thyroid gland. *J. Clin. Endocrinol. Metabol.* **11**, 1157–1165.

BLOCK M. A., HORN R. C. and BRUSH B. E. (1960) The place of total thyroidectomy in surgery for thyroid carcinoma. *Arch. Surg.* **81**, 236–243.

CADY B., SEDGWICK E. C., MEISSNER A. W. et al. (1976) Changing clinical, pathologic, therapeutic and survival patterns in differentiated thyroid carcinoma. *Ann. Surg.* **184**, 541–552.

CAMPBELL D. J. and SAGE R. H. (1975) Thyroid cancer: twenty years' experience in a general hospital. *Br. J. Surg.* **62**, 207–214.

CLARK R. L., COLE V. W. and FULLER L. M. (1967) *Cancer of Head and Neck.* Baltimore, Williams & Wilkins, p. 293.

CLARK R. L., HILL C. S. JUN. and WHITE E. C. (1969) *Thyroid Cancer.* New York, Springer-Verlag, pp. 259-266.

COPE O., DOBYNS B. M., HAMLIN E. et al. (1949) What thyroid nodules are to be feared? *J. Clin. Endocrinol. Metabol.* 9, 1012–1022.

CRILE G. JUN. (1971) Changing end results in patients with papillary carcinoma of the thyroid. *Surg. Gynecol. Obstet.* **132**, 460–468.

CRILE G. and DEMPSEY W. S. (1949) Indications for removal of non-toxic nodular goiter. *JAMA* **139**, 1247–1250.

DAJILLIAN M., BEAHRS O. H. and DEVINS K. D. (1974) Intraluminal involvement of the larynx and trachea by thyroid cancer. *Am. J. Surg.* **128**, 500–504.

DONIACH I. (1969) Epidemiology of thyroid cancer. *J. R. Coll. Surg. Edinb.* **14**, 261–262.

HAROLD C. C. and WRIGHT J. (1966) Management of surgical hypoparathyroidism. *Am. J. Surg.* **112**, 484–487.

HEITZ P., MOSER H. and STAUB J. J. (1976) Thyroid cancer. *Cancer* **37**, 2329–2337.

HIRABAYASHI R. N. and LINDSAY S. (1961) Carcinoma of the thyroid gland: a statistical study of 390 patients. *J. Clin. Endocrinol. Metabol.* **21**, 1596–1610.

MCLINTOCK J. C. (1968) Thyroid neoplasia. In: *Proceedings of the Second Imperial Cancer Research Fund Symposium.* London, Academic Press, pp. 80–96.

MA M. K. G., NG W. L. and ONG G. B. (1975) Drill biopsy of the thyroid gland. *Aust. NZ J. Surg.* **45**, 290–293.

RUSSELL W. O., IBANEZ M. L. and CLARK R. L. (1969) *Thyroid Cancer.* New York, Springer-Verlag, pp. 14–25.

SCOTT J. S. (1974) Nonsurgical treatment of thyroid tumours and its results. *Proc. R. Soc. Med.* **67**, 1106–1107.

TAYLOR S. (1974) Thyroid cancer: surgical methods and treatment—their indications and value. *Proc. R. Soc. Med.* 67, 1105–1106.

THOMPSON N. W., OLSEN W. R. and HOFFMAN G. L. (1973) The continuing development of the technique of thyroidectomy. *Surgery* **73**, 913–927.

TOLLEFSON J. R. and DE COSSE J. J. (1963) Papillary carcinoma of the thyroid recurrence in the thyroid gland after initial surgical treatment. *Am. J. Surg.* **106**, 728–734.

WAHNER H. W., CUELLO C., CORREA P. et al. (1966) Thyroid carcinoma in an endemic goiter area, Cali, Colombia. *Am. J. Med.* **40**, 58–66.

WATERHOUSE J. A. H. (1974) *Cancer Handbook of Epidemiology and Prognosis.* Edinburgh, Churchill Livingstone, p. 174.

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Experiences with head injuries in a regional neurosurgical unit

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SUMMARY

A review of all patients with major head injuries transferred to a regional neurosurgical unit for the years 1975 and 1976 has been carried out for comparison with the total number of patients with head injury admitted to district general hospitals of the region. Fifty-four per cent of patients admitted to the neurosurgical unit have resumed their old occupation and 20 per cent died. The significance of these figures is discussed, particularly in the light of the need for a more comprehensive policy for treating head injuries within the United Kingdom.

IN the United Kingdom the number of patients admitted to hospital suffering from a head injury has reached epidemic proportions. For example, in 1972 the figure was 142 000 (*Epidemiology of Head Injuries in England and Wales*, 1976). The majority ultimately make full recoveries. However, there is a group who either have a disastrous head injury from the outset or develop major complications which require neurosurgical treatment. In an attempt to enumerate the latter, the extent of therapy required and the success rate for all this effort, a retrospective survey has been carried out on all cases with head injuries transferred to the Mersey Regional Department of Surgical Neurology for the years 1975 and 1976, thereby allowing a minimum follow-up time of 1½ years.

Policy

The Mersey Regional Department of Surgical Neurology is the sole neurosurgical unit responsible for the Mersey Regional Health Authority, the Area Health Authorities of Clwyd and Gwynedd and the Isle of Man Health Board. There is a potential catchment area of 3·25 million. Cases of minor head injury are not transferred. Head injuries are transferred at the request of surgeons and physicians in the district general hospitals, who are encouraged to telephone and discuss problems. Advice is given over the telephone and either further therapy is undertaken at the district general hospital or the patient is transferred. The reasons for transfer are:

1. Deterioration in level of consciousness and/or a worsening neurological deficit.
2. Unconsciousness for more than 4 h after injury and severe problems for the staff at the district general hospital.
3. Surgical problems such as CSF rhinorrhoea or a depressed skull fracture.
4. Long term complications such as chronic subdural haematoma and post-traumatic hydrocephalus.

Patients and methods

Two hundred and forty-eight patients were transferred to the neurosurgical unit from January 1975 to December 1976: 93·5 per cent came in as emergencies and 6·5 per cent as a result of late complications developing more than 10 days after head injury. All survivors have been followed up for periods in excess of 18 months but 22 were lost to long term study.

Therapeutic considerations

Skull X-rays had usually been performed in the referring district general hospital. In a rapidly deteriorating patient with a suspected intracranial haematoma burr hole exploration was done followed, if necessary, by exploratory craniotomy. If it was thought that there was time for the investigation, angiography was carried out; 45 per cent of the admissions were so investigated. This series antedates computerized axial tomography, which has now totally replaced angiography. All haematomas, whether subdural, extradural or intracerebral, causing displacement of the brain and/or a rise in intracranial pressure were explored surgically and evacuated either through burr holes or a craniotomy. Depressed fractures were explored and elevated. All unconscious patients and patients in whom it was considered that there was evidence of cerebral contusion and/or laceration were treated with dexamethasone. Intermittent intravenous injections of 20 per cent mannitol were used for severe episodes of raised intracranial pressure. If there was any question of respiratory insufficiency as judged by blood gases, intermittent positive pressure respiration was used for the first few days through an endotracheal tube and a tracheostomy was performed if continuing ventilation was required thereafter. All unconscious patients were so treated for the first 24 h and, provided that some progress was made, treatment was continued. All patients were so treated for the first 24 h and provided some progress was made, treatment was continued. In patients exhibiting evidence of cerebral death after a minimum of 24 h therapy, life support systems were withdrawn.

Results

Age and sex

There were 185 males and 63 females. *Fig.* 1 analyses the age distribution of the patients and clearly demonstrates that the patients most commonly encountered are in the first three decades of life. Younger patients are frequently seen, but they are less likely to die (*Fig.* 2).

Mode of injury

The mode of head injury usually falls into one of five main subdivisions (*Table I*). Injury at home and in road traffic accidents is more frequent than during sport or at work.

Clinical condition

An almost equal number of patients were found to be conscious, drowsy or unconscious at the initial admission and following transfer to the neurosurgical unit. However, there was an increase of 21 per cent in the number of patients who developed neurological deficit in the time elapsing between admission to the district general hospital and transfer to the neurosurgical unit (*Table II*).

Classification and treatment

Any classification of head injuries has to be crude; for example, an extradural haematoma may well be associated with *contre-coup* contusion. Based upon clinical, radiographic and surgical findings, the primary

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Table I: MODE OF INJURY

	1975	1976	Whole series (%)
Road traffic accident	40 (34%)	43 (33%)	33
Sport	8 (7%)	14 (11%)	9
Home	39 (33%)	25 (19%)	26
Work	7 (6%)	6 (4%)	5
Misc.	23 (20%)	43 (33%)	27
Total	117 (100%)	131 (100%)	100

Table II: CLINICAL CONDITION

Place of examination	Conscious	Drowsy	Unconscious	Neurological deficit
District general hospital	88 (37)	66 (28)	84 (35)	91 (37)
Neurosurgical department	86 (35)	67 (27)	95 (38)	145 (58)

Figures in parentheses are percentages.

Table III: DIAGNOSES

	1975	1976	Whole series (%)
Concussion	29 (25%)	14 (11%)	17
SDH	33 (28%)	41 (31%)	30
EDH	14 (12%)	20 (15%)	14
Other	41 (35%)	56 (43%)	39
Total	117 (100%)	131 (100%)	100

SDH, Subdural haematoma; EDH, extradural haematoma.

Table IV: SHORT TERM OUTCOME*

	1975	1976	Whole series (%)
Improved	94 (80%)	90 (68%)	74
Static	6 (5%)	10 (8%)	7
Death	17 (15%)	31 (24%)	19
Total	117 (100)%	131 (100%)	100

* Within 10 days of injury.

Table V: LONG TERM OUTCOME*

	1975	1976	Whole series (%)
Back to old job	56 (56%)	66 (52%)	54
Slightly disabled	7 (7%)	19 (15%)	11
Disabled: independent	4 (4%)	2 (2%)	3
Disabled: dependent	8 (8%)	— —	4
Hospitalized 3 mth after injury	3 (3%)	4 (3%)	3
Died	22 (22%)	35 (28%)	25
Total	100† (100%)	126‡ (100%)	100

* More than 10 days after injury.
† No reply from the GP in 17 cases.
‡ No reply from the GP in 5 cases.

Table VI: MORTALITY RATES IN VARIOUS SERIES

Study	Mortality rate (%)
Kerr, 1971	10·8
Klonoff and Thompson, 1969	13·6
Jennett et al., 1977	14·0
Present series, 1978	19·7

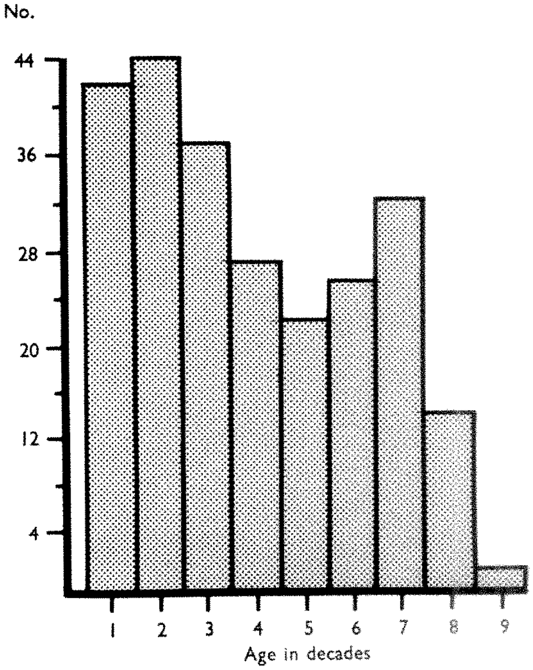


Fig. 1. Age distribution by decade of all cases of head injury admitted to the Mersey Regional Department of Surgical Neurology.

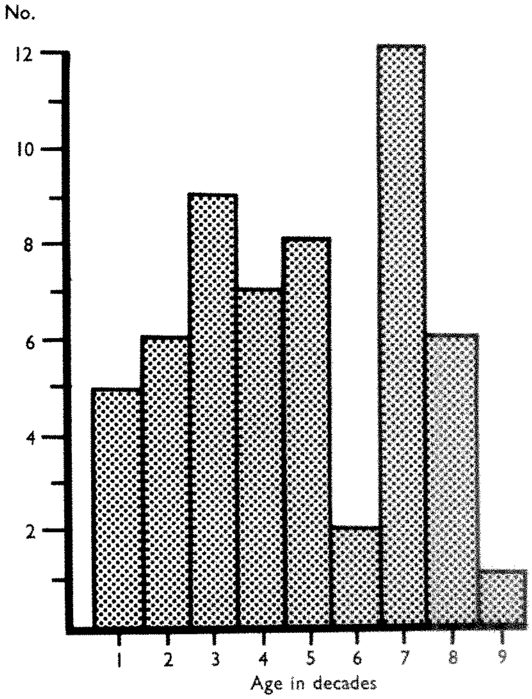


Fig. 2. Age distribution by decade of those dying from a head injury.

major diagnosis has been listed in an attempt to give a rough idea of the relative numbers in the main groups (*Table III*). The group designated 'concussion' comprised those whose period of unconsciousness was in excess of 24 h and was associated with a prolonged post-traumatic amnesia, but who did not develop focal neurological deficit. The group entitled 'other' includes those patients with both depressed levels of consciousness and focal neurological deficit suggestive of either focal or multiple brain contusions and lacerations. Not quite two-thirds (61 per cent) of the patients underwent surgical exploration. Forty-four per cent of patients had an intracranial haematoma, 14 per cent being extradural and 30 per cent subdural.

Clinical outcome

The overall mortality rate was 20 per cent. Twenty-one patients out of a total of 49 were adjudged to be suffering from brain death upon arrival at the neurosurgical unit. Eighteen patients talked and died (Reilly et al., 1975). Analysis of the records and autopsy reports indicates that 14 of these deaths might have been prevented by earlier transfer and treatment. The short term outcome (within 10 days of head injury) is shown in *Table IV* and the long term outcome (more than 6 months after injury) is shown in *Table V*.

Discussion

The age and sex distribution of patients in this series are very similar to figures produced by others (Klonoff and Thompson, 1969; Kerr et al., 1971; *Epidemiology of Head Injuries in England and Wales*, 1976; Jennett et al., 1977). Although road traffic accidents were the major cause of injury in this study, the high incidence of accidents in the home should be noted.

The numbers and outcome in this series must be interpreted against the background of all head injuries within the catchment area. In 1975 and 1976, 226 people died at the scene of the accident, 20 273 patients with head injury were admitted to the district general hospitals and 266 (1·3 per cent) of these died there. In all, 248 patients (1·2 per cent) with severe head injuries were transferred to the Regional Neurosurgical Unit where 19·7 per cent died. It is probable that the majority of patients dying in the district general hospitals had suffered from irreparable brain damage and would not have survived irrespective of treatment. However, some might have been saved. The first 12 h after a severe head injury constitute a particularly critical period and a great deal more study is needed at this level. To this end, a more detailed retrospective study of these 266 patients is at present being undertaken.

It is in the light of these remarks that the mortality rate in different series (*Table VI*) should be viewed. The Mersey Regional Neurosurgical Unit is able to admit only 1·2 per cent of all head injury cases within its catchment area. In the Scottish study the comparable figure for 1974 was nearer 4 per cent (Jennett et al., 1977). Unless the head injuries sustained in Scotland are more severe than those in England and Wales, it seems that there may be some dilution from slightly less severely head injured patients in the Scottish series. This is not to say whether the Scottish transfer ratio is right or wrong. Further study is needed to assess which patients should be transferred to a neurosurgical unit. It is clear, however, that with the numbers of head injuries occurring in the United Kingdom, patients with minor concussion are not likely to be seen by neurosurgeons. However, those dealing with head injuries should be aiming at an ideal whereby any severely injured patient who is deteriorating is transferred immediately. In addition, trial policies—say of transferring all patients who are still unconscious 6 h after the accident—may establish yardsticks that may help improve results.

It is unlikely that any single therapeutic measure is going to make much difference to the outcome. Regimens of treatment and the enthusiasm or otherwise of those surgeons dealing with head-injured patients are probably more important. The two means whereby the mortality/morbidity rate may be reduced are in the areas of accident prevention and the acute treatment in the district general hospitals. As to the former, it should be stressed that in 1975 and 1976 in Merseyside and North Wales, 590 people lost their lives as a result of a head injury.

Patients with head injuries comprised 10 per cent of all patients admitted to the Mersey Regional Department of Surgical Neurology and 75 per cent of emergency admissions. These patients absorb a great deal of time and effort. We are, therefore, encouraged to find that 54 per cent of all such patients resumed their previous occupations but at the same time we recognize that this is a crude criterion by which to judge the true extent of recovery after a major head injury.

It is true to say that there has never been a definitive policy for the treatment of head injuries in the United Kingdom. Policies have evolved locally by varying degrees of liaison between regional neurosurgical centres and district general hospitals depending upon available resources and attitudes of mind. We are disturbed at the number of patients with head injuries dying in the district general hospitals and submit these facts in the hope that they will make a contribution to the very necessary discussions that should take place regarding the management of head injuries in the United Kingdom.

Acknowledgements

The Statistical Department of the Mersey Regional Health Authority and the office of Population Censuses and Surveys very kindly provided the figures for the background information. The cases admitted to the regional unit were under the care of Mr R. H. Hannah, Mr C. B. Sedzimir, Mr J. B. Miles and Mr R. V. Jeffreys. The authors are grateful to them for allowing their case material to be included. We are grateful to Miss L. C. Power for secretarial assistance.

References

Epidemiology of Head Injuries in England and Wales. (1976) (The Field Report). London, HMSO.

JENNETT B., MURRAY A., MCMILLAN R. et al. (1977) Head injuries in Scottish hospitals. Scottish Head Injury Management Study. *Lancet* **2**, 696–698.

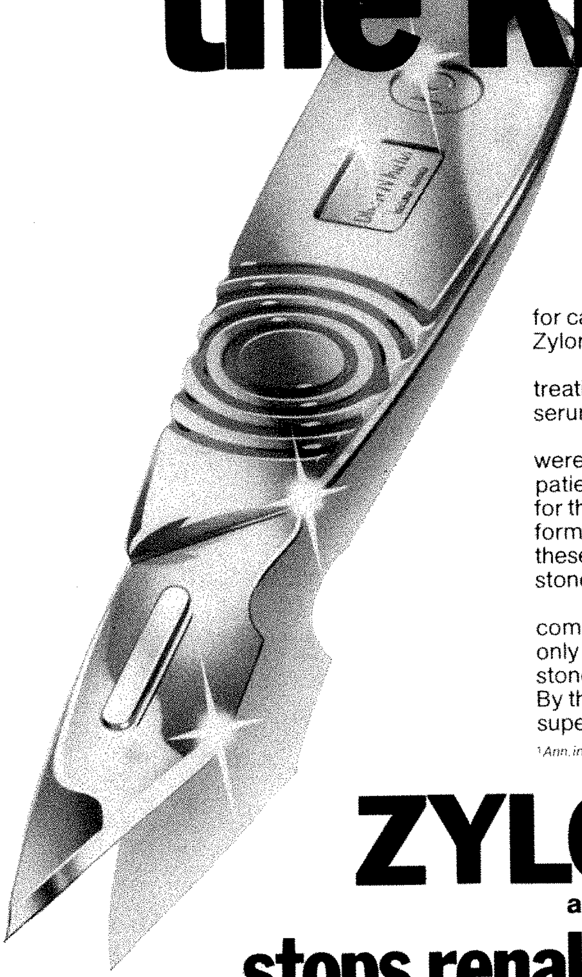
KERR T. A., KAY D. W. K. and LASSMAN L. D. (1971) Characteristics of patient, type of accident, and mortality in a consecutive series of head injuries admitted to a neurosurgical unit. *Br. J. Prev. Soc. Med.* **25**, 179–185.

KLONOFF H. and THOMPSON G. B. (1969) Epidemiology of head injuries in adults, a pilot study. *Can. Med. Assoc. J.* **100**, 235–241.

REILLY P. L., ADAMS J. H., GRAHAM D. I. et al. (1975) Patients with head injury who talk and die. *Lancet* **2**, 375–380.

Paper accepted 5 March 1979.

mightier than
the knife



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[1] *Ann. intern. Med.* (1977), **87**, 404. [2] *Brit. med. J.* (1977), **2**, 1302. [3] *J. Urol.* (1977), **117**, 690.

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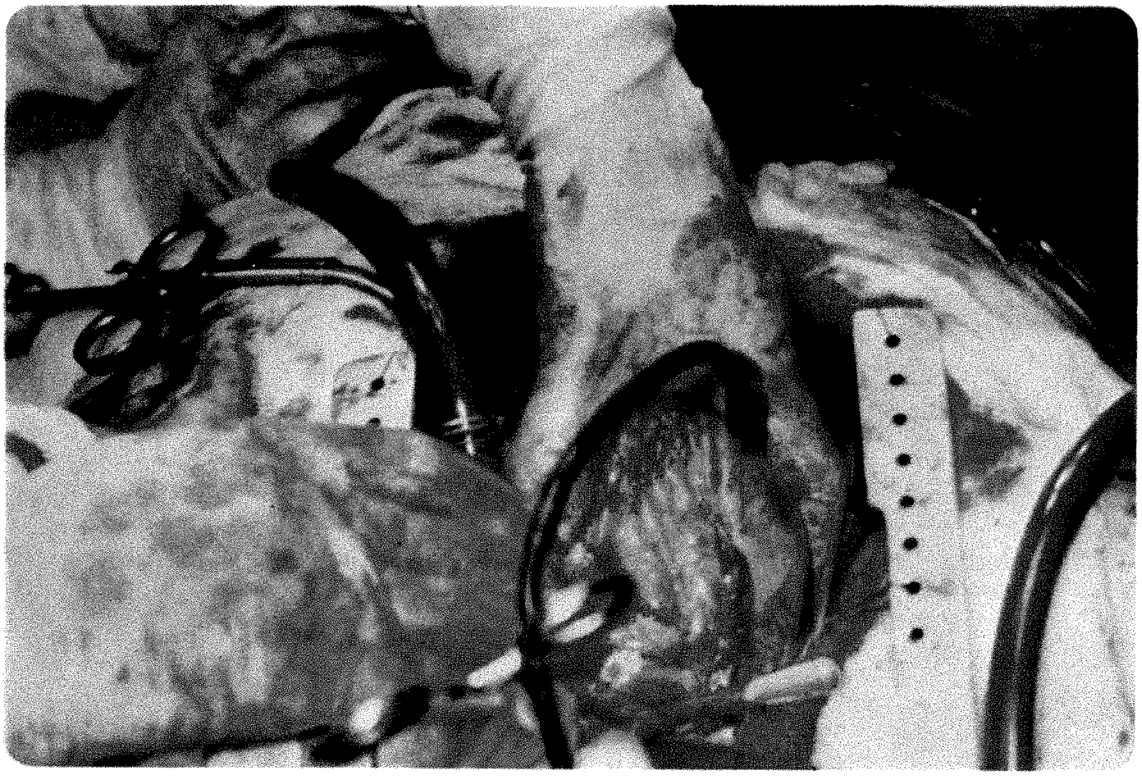

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1 Brit med J (1978) **1**, 1603
2 Thorax (1978), 33 **1**, 130
3 Brit med J (1978) **2**, 536
4 Brit med J (1970), **4**, 455
5 Zbl Bakt Hyg I Abt Orig A (1976), **236**, 235

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Magnapen Capsules: Black and turquoise capsules overprinted "Magnapen" containing 250mg ampicillin as Ampicillin Trihydrate B.P. with 250mg flucloxacillin as flucloxacillin sodium.
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Experience in the management of 50 consecutive penetrating wounds of the heart

ASHIS K. MANDAL, S. OKPAKO AWARIEFE AND SONNY S. OPARAH*

SUMMARY

Fifty patients with penetrating wounds of the heart were grouped into three categories, based on the clinical severity of the injuries.

Gunshot wounds consistently resulted in a higher mortality than knife wounds. Central venous pressure (CVP) was the single most important means of determining cardiac tamponade. The survival rates in the respective groups were 6, 79 and 100 per cent. The improved survival in our series was due to a rapid transportation system, increased awareness of the significance of cardiac injuries and an aggressive surgical approach.

SINCE Rehn's first successful cardiorrhaphy in 1896 (Balance, 1920), the management of penetrating cardiac injuries has alternated between direct surgical intervention and pericardiocentesis. Disappointed by the high operative mortality of 50 per cent, Blalock and Ravitch in 1943 advocated non-operative treatment of selected cases of cardiac wounds. This approach to therapy has also been advocated by others (Isaacs, 1959; Beall et al., 1961). In recent years, the trend has shifted to more aggressive treatment (Yao et al., 1968; Borja et al., 1970; Beall et al., 1972; Anagnostopoulos and Kittle, 1973; Bolanowski et al., 1973; Rasaretnam and Paul, 1974; Maynard et al., 1975). Despite early surgical intervention, the mortality rate remains inordinately high. The purpose of this retrospective study is to evaluate the factors that influence the survival rate.

Patients and methods

This retrospective study comprised 50 consecutive cases of penetrating injury of the heart treated at Martin Luther King Jr General Hospital from March 1972 to March 1978. There were 30 stab wounds and 20 gunshot wounds. Forty-six of the patients were men and 4 women. Their ages ranged from 12 to 53 years with a mean of 26 years. These patients were divided into three clinical groups as suggested by Steichen et al. (1971). Group A consisted of 18 'lifeless' patients who were received without blood pressure, pulse or respiration and the pupils were usually fixed and dilated. Seven (39 per cent) of these had stab wounds and 11 (61 per cent) had gunshot wounds (*Table I.*) All the patients required immediate thoracotomy. Group B consisted of 24 patients who underwent urgent thoracotomy. These patients were admitted in varying degrees of shock and cardiac tamponade. Seventeen (71 per cent) of these had stab wounds and 7 (29 per cent) had gunshot wounds. Group C comprised 8 patients who were received in a stable, normotensive state, 6 (75 per cent) of them having sustained stab wounds and 2 (25 per cent) gunshot wounds. The only evidence suggestive of cardiac injury in this group of patients was the presence of precordial wounds with elevated central venous pressure and/or electrocardiographic changes.

Table I: CLINICAL CLASSIFICATION IN CORRELATION WITH TYPE OF INJURY

Group	Stab wounds	Gunshot wounds	Total
A	7 (39)	11 (61)	18 (36)
B	17 (71)	7 (29)	24 (48)
C	6 (75)	2 (25)	8 (16)
Total	30 (60)	20 (40)	50 (100)

Figures in parentheses are percentages.

Management

All patients arrived in the emergency room within 1 h of the injury. They were initially treated in the critical room, which is a specially designated area of the emergency room equipped with facilities for emergency surgical procedures. Patients in groups A and B were immediately intubated and received assisted ventilation. Simultaneously, at least three intravenous lines were inserted using large bore needles (no. 16 gauge). One of these lines was a percutaneous central venous line. Blood was drawn for grouping and cross-matching, complete blood count and estimation of electrolytes and arterial blood gases. A Foley catheter was inserted and an electrocardiogram obtained. Hypovolaemia was initially treated with lactated Ringer's solution, 5 per cent albumin and O-negative blood until cross-matched blood was available. Haemothorax or haemopneumothorax if present was treated by tube thoracostomy with water-seal drainage. Two thousand five hundred units of heparin were added to the drainage bottle in case there was need for autotransfusion (Mattox et al., 1975; Koch et al., 1977).

Group A patients underwent immediate thoracotomy in the emergency room for pericardiotomy to relieve cardiac tamponade and to perform manual cardiac massage and myocardiorrhaphy. Other injuries were repaired in the main operating theatre.

In group B, 12 of the 17 stab wound cases and 3 of the 7 gunshot wounds had clinical evidence of cardiac tamponade with a CVP greater than 14 cmH_2O and hypotension. Two patients with stab wounds had blood pressures greater than 100 mmHg systolic with CVPs greater then 30 mmH_2O. All 15 patients with the clinical evidence of cardiac tamponade underwent pericardiocentesis via the left xiphicostal angle. The amount of blood obtained from pericardiocentesis varied from 10 to 150 ml.

The indications for thoracotomy were the presence of a precordial wound, thoracic or extrathoracic injuries from high velocity missiles which are likely to injure the heart, distended neck veins and an elevated CVP or low CVP in the face of hypovolaemia. The average time interval between arrival in the emergency room and thoracotomy was 45 min. All except 2 patients underwent anterolateral thoracotomy, the remaining 2 having a median sternotomy. Cardiopulmonary bypass was required in only 2 patients. Active bleeding from a cardiac chamber was controlled by local pressure with a finger. Occasionally the bleeding was controlled with the help of a 20 F Foley catheter which was introduced into the heart through the wound, the balloon was inflated and traction applied to the catheter so that the balloon occluded the leaking wound in the cardiac wall. The cardiac wound was repaired with non-absorbable 2/0 or 3/0 sutures in horizontal mattress stitches or 'U' horizontal mattress stitches to avoid injury of the coronary arteries. Teflon or tissue pledgets were used to buttress the stitches. In cases of very active bleeding, finger compression of the base of the heart through the transverse sinus was required to slow down bleeding in order to facilitate

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Table II: CLINICAL PICTURE OF PENETRATING CARDIAC INJURIES

Signs and symptoms	Stab wounds	Gunshot wounds	Total (%)
Distended neck veins ($CVP > 14\ cmH_2O$)	15	7	22 (69)
Hypotension ($BP < 90$ mmHg)	13	7	20 (63)
Muffled heart sounds	15	4	19 (59)
ECG abnormality	16	3	19 (59)
Dyspnoea/cyanosis	12	2	14 (44)
Cardiomegaly on chest X-ray	9	3	12 (38)

Table III: LOCATION OF INJURIES IN CORRELATION WITH MORTALITY

Location	Group A SW*	Group A GSW*	Group B SW*	Group B GSW*	Total (%)	Total died (%)
RA	1 (1)	3 (3)	2 (1)	3 (3)	9 (24)	8 (89)
RV	2 (1)	4 (4)	5 (0)	2 (1)	13 (34)	6 (46)
LA	— (—)	— (—)	1 (1)	— (—)	1 (3)	— (—)
LV	4 (4)	7 (7)	10 (0)	2 (1)	23 (61)	12 (52)

RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.
SW, Stab wounds; GSW, gunshot wounds.
* Numbers of cases who died are shown in parentheses.

Table IV: CLINICAL CLASSIFICATION IN CORRELATION WITH TYPE OF INJURY AND SURVIVAL

Type of injury	Group A No.	Group A Survival	Group B No.	Group B Survival	Group C No.	Group C Survival
SW	7	1 (14)	17	16 (94)	6	6 (100)
GSW	11	— (—)	7	3 (43)	2	2 (100)
Total	18	1 (6)	24	19 (79)	8	8 (100)

SW, Stab wounds; GSW, gunshot wounds.
Figures in parentheses are percentages.

Table V: REVIEW OF THE LITERATURE IN PENETRATING CARDIAC INJURIES

Series	Stab wounds No. of patients	Stab wounds Mortality	Gunshot wounds No. of patients	Gunshot wounds Mortality	Overall mortality (%)
(*a*)	97	11 (11·3)	5	2 (40·0)	13·0
(*b*)	80	19 (23·7)	14	8 (57·1)	30·6
(*c*)	71	16 (22·5)	9	3 (33·3)	24·0
(*d*)	48	11 (22·9)	38	12 (31·5)	27·0
(*e*)	54	9 (16·6)	—	— (—)	16·6
(*f*)	30	7 (23·3)	7	2 (28·6)	24·3
(*g*)	192	40 (20·8)	77	35 (35·0)	24·9
(*h*)	—	— (—)	27	7 (25·9)	25·9
(*i*)	34	5 (15·0)	10	6 (60·0)	25·0
(*j*)	11	2 (18·2)	22	7 (31·8)	27·2
(*k*)	54	6 (11·1)	44	12 (27·3)	18·4
(*l*)	23	1 (4·3)	9	4 (44·4)	15·6

Figures in parentheses are percentages.
(*a*) Von Berg et al. (1961); (*b*) Jones and Helmsworth (1968); (*c*) Yao et al. (1968); (*d*) Sugg et al. (1968); (*e*) Borja et al. (1970); (*f*) Steichen et al. (1971); (*g*) Beall et al. (1972); (*h*) Carrasquilla et al. (1972); (*i*) Bolanowski et al. (1973); (*j*) Mattox et al. (1974); (*k*) Symbas et al. (1976); (*l*) Mandal et al. (present series).

suturing (Beck, 1926). Atrial wounds were controlled with vascular clamps before repair.

Group C patients had electrocardiogram changes suggestive of myocardial injury in 4 of 6 stab wound cases and 1 of 2 gunshot wounds. The only patient in this group who later required thoracotomy had sustained a stab wound to the fourth left intercostal space in the midclavicular line. He was initially normotensive with normal CVP. Following 5 days of close observation the patient was discharged but was readmitted 3 weeks later with persistent chest pain and dyspnoea on exertion. The CVP at this time was elevated and pericardiocentesis produced 350 ml of serosanguineous fluid. At thoracotomy only blood clot and fibrin were found within the pericardium. Five out of 8 patients in this group required tube thoracostomy for haemothorax or haemopneumothorax.

The most frequently presenting sign in patients in groups B and C (32 patients) was distended neck veins with a CVP greater than 14 cmH_2O this was noted in 22 cases (69 per cent). The second most frequent finding was hypotension in 20 (63 per cent). Muffled heart sounds and electrocardiogram abnormality were each noted in 19 cases (59 per cent). Dyspnoea/cyanosis and cardiomegaly on a chest radiograph were the least frequently noted findings and least reliable signs of cardiac injury. The presence or absence of pulsus parodoxus was not recorded (*Table II*).

Results

Among the patients who underwent thoracotomy, one or more cardiac chambers were involved in 38 patients. Twenty-three (61 per cent) of these cases involved the left ventricle with a mortality of 52 per cent. The right ventricle was involved in 13 (34 per cent) with a 46 per cent mortality. The left atrium was involved in only one case who survived and the right atrium was involved in 9 patients with 89 per cent mortality. Multiple chamber involvement was present in most cases. In patients who had only one cardiac chamber involved the mortality rate was 29 per cent whereas in those with multiple injuries the mortality rate rose correspondingly (*Table III*).

Associated injuries were more frequent in group A. There was a variety of intrapericardial injuries, such as injury to the coronary arteries, aorta and pulmonary trunk and traumatic ventricular septal defect, and in each such patient the mortality was 100 per cent. There were also superior vena cava, azygos vein and extrapericardial aortic injuries in group A. These associated injuries were more frequent in cases with gunshot injuries than in those with stab wounds. There was a consistently higher survival rate among the stab wound cases than the gunshot wounds (*Table IV*). The survival rate in group A for patients with stab wounds and gunshot wounds was 14 and 0 per cent respectively while that of group B patients was 94 and 43 per cent respectively. All the patients in group B survived. When both stab wounds and gunshot wounds were combined the survival rate for groups A, B and C were 7, 79 and 100 per cent respectively.

Discussion

With the easy availability of hand guns the incidence of trauma due to high velocity missiles has increased significantly (Beall et al., 1972; Carrasquilla et al., 1972; Symbas et al., 1976; Szentpetery and Lower, 1977). Martin Luther King Jr General Hospital is located in South Central Los Angeles where homicide is one of the major causes of death (Haynes et al., 1973; Mandal et al., 1976). During the period under study, a total of 611 patients with penetrating chest injuries received treatment and 50 (8 per cent) of these patients sustained penetrating cardiac wounds. This is in contrast to the report of Siemens et al. (1977), who found an incidence of 16 per cent. In this series of 50 penetrating cardiac injuries, 35 per cent of the cases were categorized as 'lifeless' (Group A). Ordinarily these cases would have been pronounced dead at the scene of injury or dead on arrival in the emergency room but because of our policy of aggressive management 9 out of these 18 'lifeless' patients (50 per cent) responded to initial surgical therapy with return of normal cardiac activity following myocardiorrhaphy and manual cardiac massage, but 8 of these subsequently died of irreversible shock. The fact that we have been able to salvage one patient is a strong testimonial to the beneficial effects of immediate thoracotomy in this type of case. Mattox et al. (1974) reported 100 per cent mortality in 11 such 'lifeless' patients out of 48 who were treated for penetrating cardiac injuries. Other reported mortality rates have varied from 50 to 67 per cent (Steichen et al., 1971; Symbas et al., 1976) (*Table V*).

Cardiac tamponade is the most important life endangering complication of penetrating cardiac wounds (Martin and Schenk, 1960; Beall et al., 1961). Sixty-nine per cent of our patients exhibited clinical signs of cardiac tamponade: this is consistent with the findings of Martin and Schenk (1960). Pericardiocentesis for the relief of tamponade is imperative as the temporizing measure that offers the best chance of survival.

The pathophysiological consequences of cardiac tamponade have been well described (Cohnheim, 1889; Starling, 1897; Metcalf et al., 1952; Isaacs et al., 1954; Martin and Schenk, 1960; Carey et al., 1967; Spodich, 1967; Poris and Gaudiani, 1975). In 1889, Cohnheim postulated that the cause of circulatory impairment in cardiac tamponade was the obstruction at the veno-atrial junction, while Starling in 1897 attributed this problem to impairment of diastolic expansion. It is now widely accepted that the diminished effective filling pressure and the mechanical limitations of the right ventricular filling are the primary mechanisms responsible for the decreased cardiac output seen in acute cardiac tamponade (Martin and Schenk, 1960; Carey et al., 1967; Spodich, 1967; Poris and Gaudiani, 1975). By increasing plasma volume one may hope to improve cardiac output (Metcalf et al., 1952; Martin and Schenk, 1960; Poris and Gaudiani, 1975). We found elevation of the CVP to be the most reliable criterion for the presence of cardiac tamponade. This concurs with the findings of other investigators (Martin and Schenk, 1960; Beall et al., 1966; Yao et al., 1968; Symbas et al., 1976). Of 32 patients who were checked for CVP elevation, 22 (69 per cent) had pressure readings of 14 cmH_2O or higher and 18 of these (82 per cent) had productive pericardiocentesis. After aspiration of as little as 10 ml of non-clotting blood from the pericardial space, patients showed dramatic improvement. Other reports confirm this response (Beall et al., 1961; Levitsky et al., 1975). A non-productive pericardiocentesis does not rule out tamponade. Four patients who had unproductive pericardial aspiration had pericardial blood clots at thoracotomy. During rapid bleeding into the pericardial space, the possibility of clot formation is much greater than during slow bleeding because of inadequate agitation of the blood by the heart during the rapid bleeding (Ransdell and Glass, 1960). Borja and co-workers (1970) have reported that up to 25 per cent of patients with documented tamponade have had non-productive pericardial aspiration.

Absence of CVP elevation does not rule out cardiac injury. In the presence of hypovolaemia the CVP may be extremely low (Neville et al., 1971; Symbas et al., 1976; Szentpetery and Lower, 1977). A normal cardiac silhouette on a chest radiograph does not rule out tamponade either, for several millilitres of blood may be present in the pericardial space and yet it may not be radiographically obvious. It is the rapidity with which the fluid accumulates and not the amount of fluid that determines how rapidly cardiac tamponade is manifested (Bolanowski et al., 1973; Szentpetery and Lower, 1977). Muffled heart sounds were also found to be equally unreliable in assessing the presence of cardiac tamponade, as were electrocardiogram changes, which were present in only 59 per cent of our patients.

Since the pathophysiological manifestations of penetrating injuries are largely dependent on the extent of the injuries, which in turn relates to the wounding agent (Levitsky, 1975), it follows that stab wounds result in lower mortality. Such was the case in this study. Except in group C, there was a consistently high mortality rate from gunshot wounds. As noted by Jones and Helmsworth (1968), this was attributed to the velocity of the missile, extent of the wound, number of holes in the heart, exsanguination, intracardiac defects and other associated injuries. As a result of the larger holes produced by bullets there is a tendency for the pericardial wounds to remain open, allowing free drainage of the pericardial blood into the thoracic cavity. Such patients present with signs and symptoms of haemorrhage, haemothorax and hypovolaemic shock rather than tamponade (Martin et al., 1960; Szentpetery and Lower, 1977).

In group B the overall mortality was 21 per cent. Several factors seem to be responsible for such low mortality. There were twice as many stab wounds as gunshot wounds in this group, in contrast to group A. These patients were brought to the emergency room at a relatively early stage and were managed by an early thoracotomy. Beall and co-workers (1966) showed that when thoracotomy was performed without delay in patients with tamponade there was a 14·6 per cent mortality whereas when cardiac arrest was allowed to set in, the mortality rose to 60 per cent. Stab wounds may seal spontaneously following the egress of a small amount of blood into the pericardial sac (Levitsky, 1975). Wounds of the atrium may produce relatively slow haemorrhage with slow development of tamponade such that the patients are able to live longer while being transported to the hospital (Jones and Helmsworth, 1968). At the turn of the century it was thought that wounds of the auricle were more fatal than those of the ventricle because of the thinness of the wall, which resulted in less tendency to close. For similar reasons, right ventricular wounds were believed to bleed continuously while left ventricular wounds were thought to bleed intermittently (Neville et al., 1971). In our series, the ventricular chambers were frequently involved regardless of the type of injury; similar findings have been noted by others (Lemos et al., 1976; Asfan and Arbulu, 1977). In a report of 323 cases of penetrating wounds of the pericardium and heart, Asfan and Arbulu found that stab wounds of the right ventricle were more frequently associated with tamponade than wounds of the left ventricle (Asfan and Arbulu, 1977). Wounds of the thick muscular ventricular myocardium also frequently presented with a large volume of pericardial fluid

(Metcalf et al., 1952; Jones and Helmsworth, 1968). Such patients showed dramatic improvement following pericardiocentesis and subsequently remained remarkably stable. Small wounds that were once occluded by clot may open up during systole when the clot is expressed (Von Berg et al., 1961). Recurrent cardiac tamponade after pericardiocentesis killed 10 of 18 patients reported by Sugg et al. (1968).

The right ventricle has been reported as being the most frequent site of injury (Jones and Helmsworth, 1968; Sugg et al., 1968; Mattox et al., 1974; Symbas et al., 1976). According to the report of Jones and Helmsworth (1968), anatomical locations of cardiac injuries were 58 per cent in the right ventricle, 20 per cent in the left ventricle and 10 per cent in the right atrium. The rationale given for this distribution is the geometry of the heart in relation to the anterior chest wall. Our study does not substantiate this finding: out of a total of 38 cases in our series in which cardiac chambers were involved, the left ventricle was affected in 61 per cent, the right ventricle in 34 per cent, the right atrium in 24 per cent and the left atrium in 3 per cent. This change in frequency of involvement of various chambers of the heart in our series compared with the reports in the literature is perhaps due to an increased incidence of gunshot injuries in the population served by our hospital. In our series the highest death rate (89 per cent) was noted in patients who had right atrial involvement. This is consistent with the reports in the literature (Neville et al., 1971). Rasaretnam, however, has reported a higher mortality with left ventricular injuries (Rasaretnam and Paul, 1974). The mortality rate is high in group A regardless of the type of injury. With an increasing trend towards early thoracotomy the mortality rate for all types of penetrating cardiac injury seems to be decreasing.

References

ANAGNOSTOPOULOS C. E. and KITTLE F. C. (1973) Penetrating wounds of the heart and great vessels. *Thorax* **28**, 142–146.

ASFAN I. and ARBULU A. (1977) Penetrating wounds of the pericardium and heart. *Surg. Clin. North Am.* **57**, 37–48.

BALANCE C. (1920) The surgery of the heart. (The Bradshaw Lecture on the Surgery of the Heart.) *Lancet* **1**, 1–5, 73–79, 134–139.

BEALL A. C. JUN., DIETHRICH E. B., CRAWFORD H. W. et al. (1966) Surgical management of penetrating cardiac injuries. *Am. J. Surg.* **112**, 686–692.

BEALL A. C. JUN., OCHSNER T. L., MORRIS G. C. et al. (1961) Penetrating wounds of the heart. *J. Trauma* **1**, 195–207.

BEALL A. C. JUN., PATRICK T. A., OKIES J. E. et al. (1972) Penetrating wounds of the heart: changing patterns of surgical management. *J. Trauma* **12**, 468–473.

BECK C. (1926) Wounds of the heart: the technic of suture. *Arch. Surg.* **1**, 205–227.

BLALOCK A. and RAVITCH M. A. (1943) A consideration of the non-operative treatment of cardiac tamponade resulting from wounds of the heart. *Surgery* **14**, 157–162.

BOLANOWSKI P. J., SWAMINATHAN A. P. and NEVILLE W. E. (1973) Aggressive surgical management of penetrating cardiac injuries. *J. Thorac. Cardiovasc. Surg.* **66**, 52–57.

BORJA A. R., LANSING A. M. and RANSDELL H. T. (1970) Immediate operative treatment for stab wounds of the heart. *J. Thorac. Cardiovasc. Surg.* **59**, 662–667.

CAREY J. S., YAO S. T., KHO L. K. et al. (1967) Cardiovascular responses to acute hemopericardium compression by balloon tamponade and acute coronary occlusion. *J. Thorac. Cardiovasc. Surg.* **54**, 65–80.

CARRASQUILLA C., WILSON R. F., WALT A. J. et al. (1972) Gunshot wounds of the heart. *Ann. Surg.* **13**, 208–213.

COHNHEIM J. (1889) *Lecture on General Pathology, Section II: The Pathology of the Circulation.* London, New Sydenham Society.

HAYNES M. A., GOTTLIEB P. and LEWIS S. (1973) Health problems in the Martin Luther King Jr Hospital Service Area. *California Med.* **118**, 105–109.

ISAACS J. P. (1959) Sixty penetrating wounds of the heart: clinical and experimental observation. *Surgery* **45**, 696–705.

ISAACS J. P., BERGULUND E. and SARNOFF S. J. (1954) The pathologic physiology of acute cardiac tamponade studied by means of ventricular curves. *Am. Heart J.* **48**, 66–67.

JONES E. W. and HELMSWORTH J. (1968) Penetrating wounds of the heart: thirty years' experience. *Arch. Surg.* **96**, 671–682.

KOCH V. L., DEFORE W. W. and MATTOX K. L. (1977) A practical method of auto-transfusion in the emergency center. *Am. J. Surg.* **133**, 770–772.

LEMOS P. C. P., OKUMURA M., AZEVEDO A. C. et al. (1976) Cardiac wounds. Experience based on a series of 121 operated cases. *J. Cardiovasc. Surg.* **17**, 1–8.

LEVITSKY S. (1975) New insights in cardiac trauma. *Surg. Clin. North Am.* **55**, 43–55.

MANDAL A. K., BOITANO M. A., MAXWELL T. M. et al. (1976) Ninety-eight penetrating vascular injuries: a review of a two and one-half year experience. *J. Trauma* **16**, 354–360.

MARTIN J. W. and SCHENK W. C. (1960) Pericardiac tamponade: newer dynamic concepts. *Am. J. Surg.* **99**, 782–787.

MATTOX K. L., BEALL A. C., JORDAN G. L. et al. (1974) Cardiorrhaphy in the emergency center. *J. Thorac. Cardiovasc. Surg.* **68**, 886–895.

MATTOX K. L., WALKER L. W., BEALL A. C. et al. (1975) Blood availability for the trauma patient auto transfusion. *J. Trauma* **15**, 663–669.

MAYNARD A., DEL L., BROOKS H. A. et al. (1975) Penetrating wounds of the heart. Review of a new series. *Arch. Surg.* **90**, 680–686.

METCALF J., WOODBURY J. W., RICHARDS V. et al. (1952) Studies in experimental pericardial tamponade. *Circulation* **5**, 518–523.

NEVILLE W. E., LYNCH R. D. and VANECKO R. M. (1971) The adult cardiac patient. In: NEVILLE W. E. (ed.) *The Care of the Surgical Cardiopulmonary Patient.* Chicago, Ill., Year Book.

PORIS W. J. and GAUDIANI V. A. (1975) Cardiac tamponade. *Surg. Clin. North Am.* **55**, 573–589.

RANSDELL H. T. and GLASS H. (1960) Gunshot wounds of the heart: a review of twenty cases. *Am. J. Surg.* **99**, 788–797.

RASARETNAM R. and PAUL A. T. S. (1974) Penetrating injuries of the heart. *Br. J. Surg.* **61**, 657–661.

REHN L. (1897) Ueber penetrirenden Herz Wunden und Hertnaht. *Arch. Klin. Chir.* **55**, 315–329.

SIEMENS R., POLK H. C., GRAY L. A. et al. (1977) Indications for thoracotomy following penetrating thoracic injuries. *J. Trauma* **17**, 497–500.

SPODICH D. M. (1967) Acute cardiac tamponade, pathology, physiology, diagnosis and management. *Prog. Cardiovasc. Dis.* **10**, 64–96.

STARLING E. H. (1897) Some points in the pathology of heart disease. *Lancet* **1**, 652–655.

STEICHEN F. M., DARGAN E. L., EFRON G. et al. (1971) A graded approach to the management of penetrating wounds of the heart. *Arch. Surg.* **103**, 579–580.

SUGG W. L., REA W. J., RECKER R. R. et al. (1968) Penetrating wounds of the heart: an analysis of 459 cases. *J. Thorac. Cardiovasc. Surg.* **56**, 531–545.

SYMBAS P. N., HARLAFTIS N. and WALDO W. J. (1976) Penetrating cardiac wounds: a comparison of different therapeutic methods. *Ann. Surg.* **183**, 377–381.

SZENTPETERY S. AND LOWER R. K. (1977) Changing concepts in the treatment of penetrating cardiac injuries. *J. Trauma* **17**, 457–461.

VON BERG V. J., MOGGI L., JACOBSON L. F. et al. (1961) Ten years experience with penetrating injuries of the heart. *J. Trauma* **1**, 186–194.

YAO S. T., VENECKO R. M., PRINTEN K. et al. (1968) Penetrating wounds of the heart: a review of 80 cases. *Ann. Surg.* **168**, 67–78.

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Percutaneous transhepatic occlusion for bleeding oesophageal varices

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SUMMARY

Using the technique described by Lunderquist et al. (1977), transhepatic injection of oesophageal varices has been performed under local anaesthesia in 9 patients with portal hypertension (11 procedures). On 2 occasions it was not possible to enter the left gastric vein. Bleeding resumed within 2 days of radiologically satisfactory occlusion in 2 patients and at 1, 3, 4 and 10 months after 4 procedures in 3 patients. Other complications included portal vein thrombosis, gross ascites and right pleural effusion. There were 2 hospital deaths, both in alcoholic patients with poor hepatic function. In spite of the apparently high morbidity we consider that there is a place for this technique in tiding over patients who are bleeding from oesophageal varices and are medically unsuitable for any surgical procedure.

ADEQUATE blood transfusion, pitressin and tamponade by a double-balloon tube control most acute episodes of bleeding from oesophageal varices and allow time for full assessment and definitive treatment. Early decompression by emergency shunt as advocated by Orloff et al. (1975) is not widely practised, most clinicians preferring early elective operation in those selected as suitable following control of bleeding and full assessment (Macpherson, 1964). Two further methods of controlling bleeding which have been practised are direct injection of the varices through a rigid oesophagoscope (Johnston and Rodgers, 1973) and transhepatic occlusion, as advocated by Lunderquist and Vang (1974). We report our preliminary experience with this latter technique with particular reference to the early complications.

Patients and methods

Patients

Nine patients were treated (*Table I*): there were 7 men and 2 women with an age range from 32 to 71 years. In all but 1 patient (*Case* 6) the indication for the procedure was recurrent bleeding despite adequate conservative management. This patient had had a previous lieno–renal shunt but had persistent large varices and the indications for the procedure were diagnostic and prophylactic rather than therapeutic. All the patients had cirrhosis, 4 presumed or proved alcoholic, 4 of unknown aetiology and 1 post-hepatitic. The grade of the liver disease is shown in *Table I* according to Child's classification, considering ascites, encephalopathy, serum bilirubin and albumin and the prothrombin time ratio. The blood transfusion requirement of each patient is given as an indication of the severity of the bleeding.

In 2 of the 9 patients (*Cases* 3 and 4) the procedure had to be repeated, in both instances for further bleeding at 17 and 4 weeks respectively. Thus, 11 procedures were performed in all.

Method

The procedure was carried out in the X-ray department with image-intensified fluoroscopic control. The position and patency of the portal vein were first established by selective coeliac and mesenteric arteriography. Percutaneous transhepatic catheterization of the portal vein was performed through the right eighth or ninth rib interspace in the mid-axillary line under basal sedation (diazepam) and local anaesthesia. Using a technique similar to that described by Lunderquist et al. (1977), a catheter (6 FG) introduced over a matching needle was passed through the liver into a large intrahepatic branch of the portal vein. In most cases this was entered after three or four passes, care being taken that the needle was not withdrawn from the substance of the liver. The needle was then withdrawn and a flexible guide wire passed through the catheter which was manipulated down the portal vein and into the splenic vein. Portal venous pressure was measured and contrast medium injected while serial films were exposed to demonstrate the portal venous system, the varices and their principal feeding vessels and other collaterals (*Fig.* 1). The main sources of supply to oesophageal and gastric varices are the left gastric vein and the short gastric veins. A pre-curved guide wire was used to position the catheter within the left gastric vein and contrast medium injected there confirmed filling of the varices from this vessel (*Fig.* 2). Occlusion of this vessel was achieved by embolization with absorbable gelatin sponge (Sterispon) (*Fig.* 3). In later patients the gelatin sponge was soaked in a sclerosant, sodium tetradecyl sulphate (STD), to induce a longer-lasting venous occlusion (Viamonte et al., 1977). Other enlarged branches of the splenic vein supplying varices can be occluded by the same method. During withdrawal of the catheter, the track through the liver was occluded

Table I: PATIENTS STUDIED

Case no.	Age (yr)	Sex	Aetiology of liver disease	Grade of liver disease	Blood transfused
1	48	M	Alcohol	B	6 l
2	32	M	Alcohol	B	8·5 l
3	52	M	Alcohol	C	8 l
4	71	M	Cryptogenic	B	4·5 l
5	69	F	Cryptogenic	B	10·5 l
6	51	M	Post-hepatitis	A	0
7	48	M	Cryptogenic	B	3·5 l
8	41	M	Alcohol	B	9 l
9	60	F	Cryptogenic	B	4 l

Table II: RESULTS

Case no.	Occlusion	Recurrent bleeding	Ascites	Pleural effusion	Outcome
1	Satisfactory	2 d			OT
2	Satisfactory		++	++	Died 5 d
3	Satisfactory	4 mth			PVT
	Unchanged				Well 11 mth
4	Satisfactory	1 mth	+	+	
	Unchanged	10 mth			OT
5	Satisfactory				Well 14 mth
6	None				Well 3 mth
7	None		+	+	L–RA
8	Satisfactory	1 d	+	+	TL, died 16 d
9	Satisfactory	3 mth			OT

OT, Oesophageal transection; PVT, portal vein thrombosis; L–RA, lieno–renal anastomosis; TL, transgastric ligation.
+ Severe but responded to medical measures.
++ Required tapping, rapid reaccumulation.

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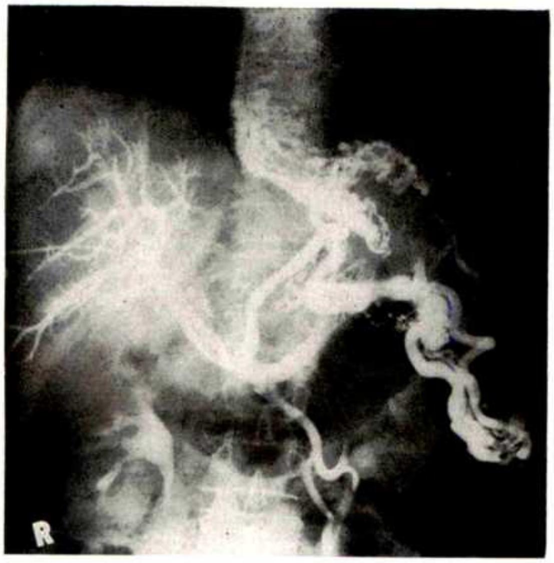

Fig. 1. Portagram showing full portal venous anatomy.

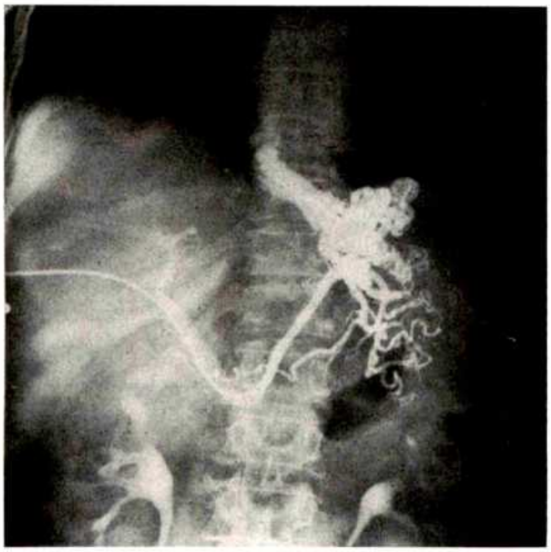

Fig. 2. Selective left gastric vein cannulation.

with further plugs of gelatin sponge to minimize the risk of bleeding from the hepatic puncture.

Results

Satisfactory occlusion of the principal feeding vessels was achieved in 8 of the 11 procedures (*Table II*). In 7 instances this occlusion was confined to the left gastric vein and in the eighth procedure, which was a second embolization, the short gastric veins were occluded. The reasons for the 3 failures were portal venous thrombosis preventing catheterization at the second procedure in *Case* 3, inability to catheterize selectively the left gastric vein in *Case* 6 due to its acute angle of entry (probably a consequence of previous surgery) and inability to advance the catheter down the portal vein, despite its patency as shown by preliminary arteriography, in *Case* 7. In this patient ascites sufficient to separate the liver from the abdominal wall contributed to the difficulty in catheter manipulation.

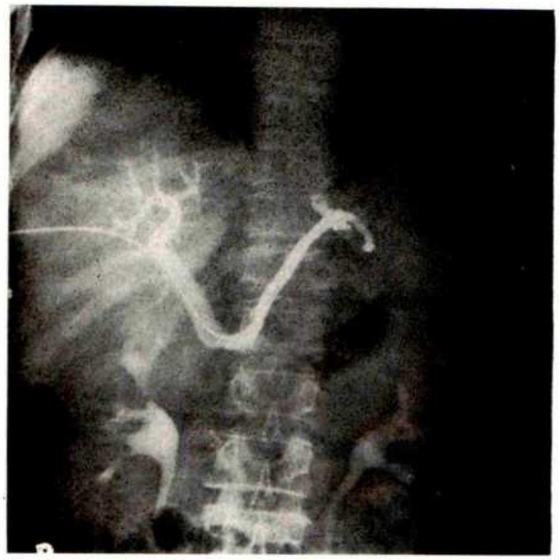

Fig. 3. Occlusion of left gastric vein.

Recurrent bleeding

Five patients bled again, 2 dramatically in the first 48 h after apparently satisfactory occlusion of the left gastric vein and 3 after a longer interval. Four patients, including the 2 early recurrences, came to surgery, 3 to oesophageal transection and 1 to a transgastric ligation. The other 2 had repeat procedures. *Case* 3 was found to have a portal venous thrombosis 17 weeks after the first injection. This precluded further occlusive measures, but the patient has not bled since. In *Case* 4 a further successful occlusion was achieved but bleeding recurred 9 months later.

Ascites and pleural effusion

There was a noticeable increase in ascites following 5 procedures in 4 patients in whom it was already present and in 3 of these patients there also developed a massive right pleural effusion. In one other patient (*Case* 3) a right pleural effusion developed without any clinical change in the ascites.

Mortality

There were 2 deaths, *Case* 2 already mentioned and *Case* 8 who bled again within 24 h and required ligation of a bleeding gastric varix. He died 16 days later from progressive hepatic failure.

Of the other 7 patients, 3 have subsequently had oesophageal transection for recurrent bleeding at 48 h, 12 weeks and 10 months respectively. All are alive 3–14 months after the transhepatic injection.

Discussion

Reported experience with transhepatic injection of oesophageal varices from other centres has shown that an occlusion rate of the order of 90 per cent can be achieved (Scott et al., 1976; Lunderquist et al., 1977; Viamonte et al., 1977) with a hospital mortality rate of 18 per cent. The incidence of recurrent bleeding in those in whom occlusion has been obtained is collectively reported as 20 per cent. Our results have been less satisfactory, 6 episodes of recurrent bleeding having occurred in 5 of the 9 patients, 2 within 48 h of the procedure and 4 at 1, 3, 4 and 10 months afterwards.

The early complications of increasing ascites and right pleural effusions, which have been significant problems in our experience, have not been reported elsewhere. Scott and his colleagues (1976) reported 5 of their 13 patients as having a right haemothorax following the procedure, but none of the other reports mention pulmonary complications. The effusions we have encountered have not been bloodstained, and there was no evidence of significant bleeding from the hepatic puncture sites. The two complications of increase in an already present ascites and the development of a right pleural effusion appear to be intimately connected. The tendency to fluid accumulation in these ill patients and the reaction of the serous membranes to the passage of the needle may be sufficient explanation of the coincidental appearance of these complications. Occlusion of portasystemic connections through the left gastric vein could lead to a temporary increase in portal venous pressure and thereby to an increased tendency to ascitic fluid formation. During hepatic puncture the pleural cavity may be traversed by the needle and cannula and a direct pleuroperitoneal communication established through which, though of small size, ascitic fluid under pressure could leak. This sequence appeared to occur in *Case* 2, who had a satisfactory occlusion and developed a very tense ascites and a rapidly accumulating right pleural effusion which undoubtedly contributed to his death. We consider that a significant degree of ascites is a contraindication to this procedure.

Manipulation of the guide wire and catheter and several injections of contrast medium probably increase the risk of portal vein thrombosis, particularly if the blood flow in that vessel is already slowed. However, this complication has not previously been reported. Lunderquist and his colleagues (1977) in an addendum to their report comment on marginal thrombus being found in the portal vein at necropsy in some of their patients, but point out that this is a common finding in this group anyway. Our *Case* 3 was found to have portal vein thrombosis at repeat examination at 4 months, this being confirmed at splenoportography, and we believe that this must be recorded as a complication of the technique.

The incidence of recanalization of occluded vessels varies widely from series to series. Early workers employed substances such as 50 per cent glucose and thrombin (Lunderquist et al., 1977), and in patients in whom occlusion was undertaken with these substances recanalization was common. Viamonte and his colleagues (1977) found that none of 10 patients occluded with Gelfoam and STD had recanalized when reassessed. Attempts at more permanent occlusion with Bucrylate (isobutyl-2-cyanoacrylate) have been reported (Rosch et al., 1975; Lunderquist et al., 1977), but follow-up reports are still awaited. Only 3 of our patients have had radiological reassessment, and none had recanalized the occluded vessels in the short term. In one case who came to necropsy complete occlusion of the left gastric vein was confirmed.

Despite the complications we have encountered, we believe that transhepatic injection of oesophageal varices is a useful additional therapeutic technique in the management of the bleeding patient with portal hypertension. Its principal advantage is that it does not require general anaesthesia and therefore can be employed in the seriously ill patient who has continued to bleed despite adequate conservative treatment. The relief it provides should be looked on as temporary for only the main feeder veins are occluded and, as with transoesophageal injection or ligation of varices, it should be followed by definitive surgery when circumstances permit. Significant ascites is, in our opinion, a contraindication to the procedure.

References

JOHNSTON G. W. and RODGERS H. W. (1973) A review of 15 years' experience in the use of sclerotherapy in the control of acute haemorrhage from oesophageal varices. *Br. J. Surg.* **60**, 797–800.

LUNDERQUIST A., SIMERT G., TYLEN V. et al. (1977) Follow-up of patients with portal hypertension and oesophageal varices treated with percutaneous obliteration of gastric coronary vein. *Radiology* **122**, 59–63.

LUNDERQUIST A. and VANG J. (1974) Transhepatic catheterisation and obliteration of the coronary vein in patients with portal hypertension and oesophageal varices. *N. Engl. J. Med.* **291**, 646–649.

MACPHERSON A. I. S. (1964) Treatment of bleeding from oesophageal varices with special reference to the use of the balloon tube. *Scot. Med. J.* **9**, 243–248.

ORLOFF M. J., CHARTERS A. C., CHANDLER J. G. et al (1975) Portacaval shunt as emergency procedure in unselected patients with alcoholic cirrhosis. *Surg. Gynecol. Obstet.* **141**, 59–68.

ROSCH J., GOLDMAN M. L. and DOTTER C. T. (1975) Experimental catheter obstruction of the gastric coronary vein. Possible technique for percutaneous intravascular tamponade of gastro-oesophageal varices. *Invest. Radiol.* **10**, 206–211.

SCOTT J., LONG R. G., DICK R. et al. (1976) Percutaneous transhepatic obliteration of gastro-oesophageal varices. *Lancet* **2**, 53–55.

VIAMONTE M., PERIERAS R., RUSSELL E. et al. (1977) Transhepatic obliteration of gastro-esophageal varices: results in acute and non-acute bleeders. *Am. J. Roentgenol.* **129**, 237–241.

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Pyloric diaphragm, antral web, congenital antral membrane—a surgical rarity?

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SUMMARY

Three cases of pyloric diaphragm in elderly patients are reported. The finding of these patients within a 2-year period (1976–8) suggests that the condition is not as rare as previously thought. Diagnosis was achieved endoscopically and the condition managed surgically.

While there has been controversy in the past over whether the disorder is acquired or congenital, the histological evidence of the cases presented here tends to suggest that it is a late presentation of a congenital abnormality.

MOST instances of pyloric obstruction in the adult are either due to stenosis from duodenal ulceration or to carcinoma. Obstruction from a congenital pyloric diaphragm (*Fig.* 1) has been reported but has been recognized by endoscopy on only a few occasions.

We report here 3 cases of pyloric diaphragm presenting for the first time in late adult life.

Case reports

Case 1: J. McR., a female aged 70 years, presented in March 1978 with a 6-month history of anorexia, occasional vomiting and weight loss. There was no history of pain, heartburn or water brash. Her past medical history was unremarkable.

The initial barium meal examination showed a grossly dilated stomach with a large food residue. A presumptive diagnosis of pyloric stenosis was made. In view of the relative lack of symptoms and absence of a previous dyspeptic history, surgical intervention was deferred and a second barium meal examination, 3 months later, suggested a pyloric diaphragm.

Two endoscopic examinations were made; the first failed to demonstrate patency of the pylorus and the second showed a smooth pinhole pyloric opening.

At laparotomy, a duodenotomy was performed and the examining finger, passed proximally, could not negotiate an antral obstruction. The duodenum itself was normal. Gastrotomy revealed a smooth antral diaphragm with a 2-mm centrally placed os through which a fine probe was passed. Antrectomy with gastroduodenal anastomosis was performed. Six months after surgery the patient remains well.

The resected specimen consisted of a portion of gastric antrum, including the pylorus, with an attached cuff of duodenum. The normal pylorus was recognized by its characteristic mucosal folds and serosal groove. A diaphragm, complete apart from a central 1–2-mm orifice, was located 1·5 cm proximal to the pylorus. The stomach wall was rather thickened proximal to the diaphragm and the gastric mucosa flattened with a pebbled appearance. There was no ulceration in either the stomach or the duodenum. Histology of the diaphragm showed a central core of submucosa covered on both proximal and distal aspects by normal gastric mucosa. These appearances are consistent with an antral diaphragm.

Case 2: M. L., a female age 77 years, presented in April 1978 with a short history of general malaise and vomiting after meals. She was pain-free, had a good appetite and her weight was steady. A barium meal examination demonstrated pyloric hold-up. Endoscopy showed a small histus hernia with an area of lower oesophageal ulceration. The gastric mucosa appeared normal but the pyloric opening was only the size of a pinhole, smooth and impossible to negotiate (*Fig.* 2). A diagnosis of a pyloric diaphragm was made.

Laparotomy revealed findings similar to those in *Case* 1. Antrectomy with gastroduodenal anastomosis was performed. The patient remains well 6 months after surgery.

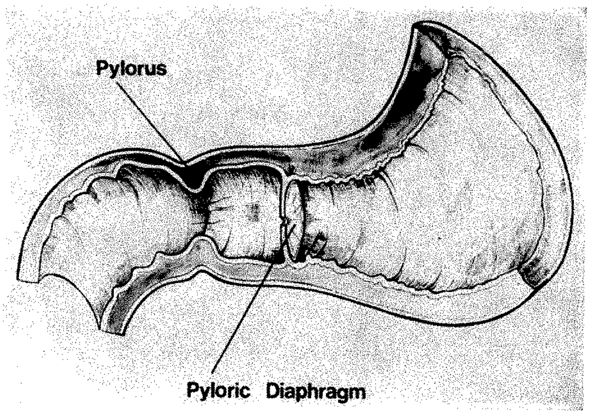

Fig. 1. Artist's impression of pyloric diaphragm.

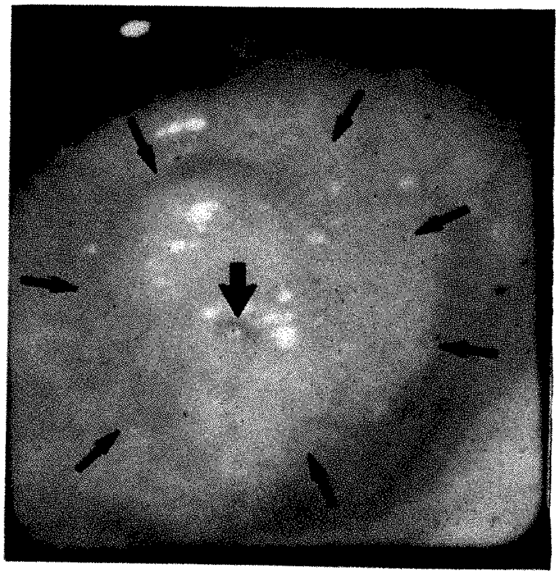

Fig. 2. Endoscopic photograph (*Case* 2) showing pinhole aperture in diaphragm (central arrow). The periphery of the diaphragm is shown (ring of arrows), peristalsis ceasing here.

The surgical specimen was essentially the same as in *Case* 1 except that the diaphragm was in the vicinity of the pylorus, which could not be separately identified. The presence of Brunner's glands in sections taken just distal to the diaphragm suggested that this was a pyloric diaphragm. There was no evidence of recent or past ulceration in either the stomach or the duodenum. Some hypertrophy of the gastric musculature was evident.

Case 3: J. G., a female aged 71 years, presented in November 1976 with a 40-year history of epigastric discomfort which has

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been treated as peptic ulceration with little relief. During the year before presentation, the pain became more severe, particularly following meals. The patient was nauseous but had never vomited.

Barium meal examination was reported as showing no evidence of peptic ulceration, but narrowing of the pylorus suggestive of a pyloric diaphragm. This was confirmed at endoscopy when a pinhole pylorus was found through which the endoscope could not be passed.

At laparotomy an advanced carcinoma of the body of the pancreas was found. The stomach was not examined. The patient died 5 weeks later.

Discussion

Congenital malformations of the stomach are exceedingly rare. Parrish et al. (1966) estimated the incidence as 1 in 1 000 000 births. Since Sames (1949) described partial atresia of the pyloric antrum due to a mucosal diaphragm, over 50 similar cases have been described (Sloop and Montague, 1967; McBee and North, 1970; Javier-Gabriel, 1976). The true incidence of this condition is difficult to assess because of differences in nomenclature (Schwartz et al., 1977), variations in classification and the wide age distribution.

Recognition of the lesion was simplified by Gerber and Aberdeen in 1965. They reviewed the literature and suggested the lesion be classified as follows:

I. Pyloric: (A) membrane; (B) atresia.

II. Antral (1 cm or more proximal to the pylorus): (A) membrane; (B) atresia.

Pyloric and antral atresias (IB and IIB) present in neonates but are much less common than duodenal atresias, and a review by Ghent and Denton in 1974 revealed only 6 cases of pyloric atresia and 11 cases of antral atresia. Both pyloric and antral membranes (IA and IIA) occur over a wide age spectrum with peak incidences in infancy and the seventh decade (Munro, 1963; Banks et al., 1967). The incidence in this series is similar to that of the Mayo Clinic, reported by Feliciano and van Heerden in 1977, in which 7 cases occurred over a 5-year period. An even greater incidence of 4–5 per year was quoted by Tanner (1967). However, Rowling (1959) failed to identify a single case in 2625 autopsy studies.

Most authors favour a congenital aetiology with failure of gut canalization in the 5th–6th embryonic week as the most likely explanation. Others suggest fetal injury with subsequent damage to the affected part (Bell et al., 1977). However, the late onset of symptoms creates doubts as to whether in fact the lesion is congenital or not. Rhind (1959), Strange (1967) and van der Reis et al. (1977), postulated an inflammatory aetiology and suggested that the lesion was due to scarring from annular ulceration of the pylorus. However, the mild inflammatory changes, such as those in *Case* 1, are generally regarded as secondary to stasis, and the uniformity of the histological appearances, with which *Cases* 1 and 2 accord, is in favour of a congenital origin.

Why a congenital condition should take 50 years to produce symptoms is difficult to explain (Dorch et al., 1976). Some suggest that those cases that present late in life are associated with edentulous mastication and indeed one case presented soon after removal of all the patient's teeth (Passalacqua and Romero, 1955). A further theory postulates that with advancing age there is a general decrease in tone in an already hypertrophied stomach (Swartz and Shepherd, 1956; Hait et al., 1972).

The clinical and laboratory findings are similar to those found in pyloric stenosis.

Barium studies frequently provide a diagnosis of pyloric obstruction, but unless the characteristic knife-like linear defect in the antrum or the appearance of a double duodenal bulb are seen, the actual cause of the pyloric obstruction cannot be clarified. Indeed, the opening in the diaphragm can easily be mistaken for the pylorus itself. Concentrated barium may obscure the signs and for this reason careful technique and double-contrast studies are advisable.

Gastroscopy was performed in all 3 cases in this series and a correct diagnosis made. The findings of a dilated stomach with a small, fixed antral aperture, normal gastric mucosa and peristalsis ceasing abruptly at the margins of the membrane fulfil the diagnostic criteria laid down by Sokol et al. (1965) and Banks and Waye (1969).

Management of this condition is surgical. Simple incision of the diaphragm has been reported (Conway, 1965). Similarly, excision of the diaphragm at its junction with the stomach wall appears to give satisfactory results (Robinson, 1967). In our series, antrectomy proved a satisfactory surgical treatment and additionally allowed full histological examination. Drainage procedures with or without vagotomy have less favourable results and simple stretching of the aperture has proved difficult (Katz, 1968; Johnson, 1971). The value of a preliminary exploratory gastrotomy or duodenotomy has been emphasized (Parrish et al., 1968).

With the advent of endoscopic diathermy techniques it may soon be possible to incise the diaphragm without resorting to laparotomy (Javier-Gabriel, 1976).

Acknowledgements

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References

BANKS P. A. and WAYE J. D. (1969) The gastroscopic appearance of antral web. *Gastrointest. Endosc.* **15**, 228–229.

BANKS P. A., WAYE J. D., WAITMAN A. M. et al. (1967) Mucosal diaphragm of the gastric antrum. *Gastroenterology* **52**, 1003–1008.

BELL M. J., TERNBERG J. L., MCALISTER W. et al. (1977) Antral diaphragm—a cause of gastric outlet obstruction in infants and children. *J. Pediatr.* **90**, 196–202.

CONWAY N. (1965) Pyloric antral mucosal diaphragm. *Br. Med. J.* **1**, 970–971.

DORCH E. R., O'NEIL F. S., GRAHAM D. Y. et al. (1976) Recognizing congenital pyloric mucosal diaphragm in the elderly. *Geriatrics* **31**, 110–112.

FELICIANO D. V. and VAN HEERDEN J. A. (1977) Pyloric antral mucosal webs. *Mayo Clin. Proc.* **52**, 650–653.

GERBER B. C. and ABERDEEN S. D. (1965) Prepyloric diaphragm, an unusual abnormality. *Arch. Surg.* **90**, 472–480.

GHENT C. N. and DENTON D. (1974) Mucosal diaphragm of the gastric antrum: case report and review of the literature. *Canad. J. Surg.* **17**, 274–278.

HAIT G. ESSELSTYN C. B. jun. and RANKIN G. B. (1972) Prepyloric mucosal diaphragm (antral web). *Arch. Surg.* **105**, 486–490.

JAIVER-GABRIEL T. (1976) Gastric antral diaphragm in an adult: case report and review. *Gastrointest. Endosc.* **23**, 88–90.

JOHNSON G. M. (1971) Gastric mucosal diaphragm in children. *Pediatrics* **47**, 916–919.

KATZ L. A. (1968) Asymptomatic mucosal diaphragm of gastric antrum. Report of a case. *Gastrointest. Endosc.* **15**, 106–107.

MCBEE J. W. and NORTH L. B. (1970) Antral mucosal diaphragm in the adult. *Gastrointest. Endosc.* **16**, 196–200.
MUNRO A. I. (1963) Prepyloric mucosal diaphragm. *Br. J. Surg.* **50**, 981.
PARRISH R. A. jun., KANAVAGE C. B., WELLS J. A. et al. (1968) Congenital antral membrane. *Surg. Gynecol. Obstet.* **127**, 999–1004.
PARRISH R. A. jun., SHERMAN H. S., MORETZ W. H. et al. (1966) Congenital antral membrane. *Surgery* **59**, 681–684.
PASSALACQUA L. A. and ROMERO C. A. (1955) Partial obstruction of the pylorus due to a mucosal diaphragm of congenital origin. *Bol. Assoc. Med. Puerto Rico* **47**, 211–215.
RHIND J. A. (1959) Mucosal stenosis of the pylorus. *Br. J. Surg.* **46**, 598–604.
ROBINSON K. P. (1967) Pyloric stenosis due to a mucosal diaphragm. *Br. J. Surg.* **54**, 397–399.
ROWLING J. T. (1959) The prepyloric septum: a rare anomaly. *Br. J. Surg.* **47**, 162–166.
SAMES C. P. (1949) A case of partial atresia of the pyloric antrum due to a mucosal diaphragm of doubtful origin. *Br. J. Surg.* **37**, 244–246.
SCHWARTZ S. E., RAWDEN D. R. and DUDGEON D. L. (1977) Antral mucosal diaphragm. *Gastrointest. Endosc.* **24**, 33–34.
SLOOP R. D. and MONTAGUE A. C. W. (1967) Gastric outlet obstruction due to congenital pyloric mucosal membrane. *Ann. Surg.* **165**, 598–604.
SOKOL E. M., SHOROFSKY M. A. and WERTHER J. L. (1965) Mucosal diaphragm of the gastric antrum. *Gastrointest. Endosc.* **12**, 20–21, 28.
STRANGE S. L. (1967) Prepyloric and pyloric mucosal stenosis. *Proc. R. Soc. Med.* **60**, 1–3.
SWARTZ W. T. and SHEPHERD R. D. (1956) Congenital mucosal diaphragm of the pyloric antrum. *J. Ky Med. Assoc.* **54**, 149–151.
TANNER N. C. (1967) Prepyloric and pyloric mucosal stenosis. *Proc. R. Soc. Med.* **60**, 3.
VAN DER REIS L., FISHER J. H. and BAKER M. (1977) The pyloric septum: acquired or congenital? *Aust. NZ J. Med.* **7**, 302–303.

Paper accepted 8 December 1978.

Br. J. Surg. Vol. 66 (1979) 574

Gastric volvulus following highly selective vagotomy: a case report

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Case report

A 60-year-old male patient underwent highly selective vagotomy with dilatation of the pylorus through an anterior gastrotomy for pyloric stenosis due to chronic duodenal ulceration. The postoperative insulin test confirmed that the vagotomy was adequate. The patient remained well for 1 year, before being readmitted with recurrent vomiting, epd gastric discomfort and two episodes of malaena which lastei 2–3 days. On clinical examination there were no physical findings and the possibility of recurrent ulceration and/or restenosis was considered.

His haemoglobin was 8·0 g/dl, the white blood count, the serum electrolytes and the urea were all within normal limits. A repeat insulin gastric secretion test confirmed an adequate vagotomy. Endoscopy could not be performed because of technical problems. A barium meal examination (*Fig.* 1) showed an organo-axial volvulus of the stomach. Laparotomy confirmed the presence of the volvulus; the greater curvature of the stomach approximately 10 cm from the pylorus was the point of rotation, and this point was densely adherent to the anterior edge of the overlying liver. There was no evidence of recurrent ulceration or stenosis. The adhesions were divided and the greater curvature was separated from the colon—the so-called colonic displacement operation (Tanner, 1968). The patient was asymptomatic when seen 9 months after the operation.

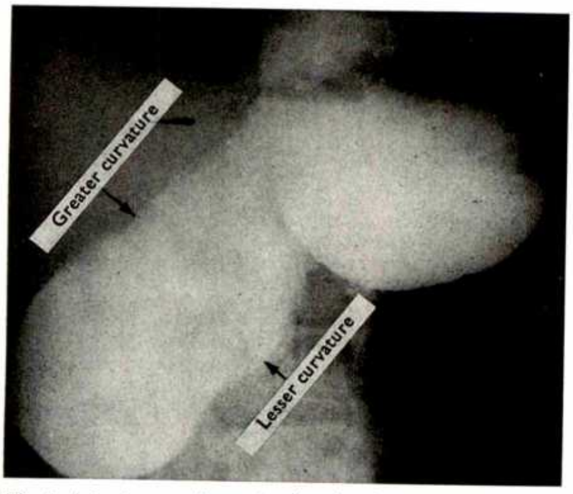

Fig. 1. A barium meal examination showing an organo-axial volvulus of the stomach.

Comment

The value of highly selective vagotomy with dilatation of the pylorus and no drainage procedure in patients with all grades of pyloric stenosis has been demonstrated (Johnson et al., 1973). However, volvulus secondary to adhesion formation has not been reported following this operation. The adhesions to the liver and a dilated hypertrophied stomach due to the previous stenosis seems to have precipitated this volvulus.

References

JOHNSON D., LYNDON P. J., SMITH R. B. et al. (1973) Highly selective vagotomy without drainage procedure in the treatment of haemorrhage, perforation and pyloric stenosis due to peptic ulcer. *Br. J. Surg.* **60**, 790–797.
TANNER N. C. (1968) Chronic and recurrent volvulus of the stomach with late results of 'colonic displacement'. *Am. J. Surg.* **115**, 505–515.

Paper accepted 20 December 1978.

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Br. J. Surg. Vol. 66 (1979) 575–576

Ingrowing toenails: the results of treatment

BERNARD V. PALMER AND ANGELA JONES

SUMMARY

Completed questionnaires were received from 208 patients on whom 245 operations for ingrowing toenails had been performed at King's College Hospital. Avulsion of a strip of nail had an 83 per cent recurrence rate, total nail avulsion 70 per cent, Zadik operations 28 per cent and wedge resections 29 per cent.

It is recommended that immediate avulsion of ingrown toenails should not be a routine practice.

In many casualty departments in this country the usual treatment for acutely inflamed ingrowing toenails is immediate avulsion of the nail. The rationale for this form of treatment is that it gives immediate relief of pain. However, it is apparent that many patients return within a few months with a recurrence of their symptoms. An attempt has been made to evaluate the efficacy of various operative treatments of ingrowing toenails in a busy district teaching hospital.

Patients and methods

A questionnaire was sent to all inpatients and casualty patients who had had operations for ingrowing toenails in King's College Hospital between 1975 and 1977. They were asked for details of their operations and whether they needed or had had any subsequent treatment for the same condition.

Two hundred and sixty-nine questionnaires were sent out in June 1978. If no reply was received, a further questionnaire was sent 4 weeks later. Two hundred and eight replies were obtained, a response rate of 77 per cent.

The patients' sex and age at the time of presentation are shown in *Fig.* 1. There were 141 male patients (67 per cent) and 67 female patients (33 per cent). The mean age of presentation was 23·8 years for males and 32·4 years for females. Forty-nine per cent of all patients were below the age of 20. There was a male : female ratio amongst the patients under 30 years of age of 2·75 : 1. Above the age of 30, the ratio was virtually 1 : 1.

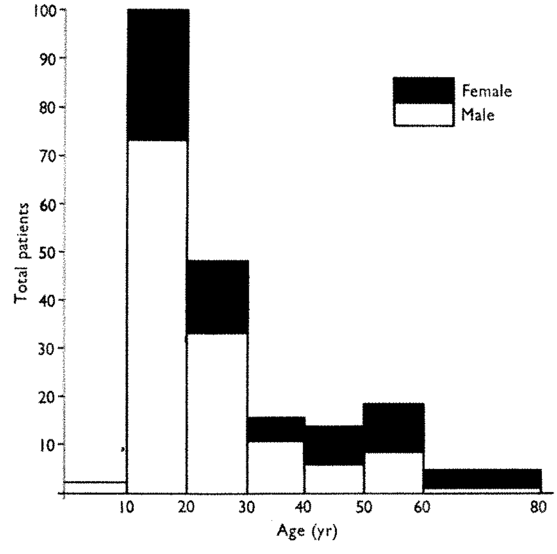

Fig. 1. Sex age distribution of the patients.

Results

Side affected

The right big toe was affected in 82 patients and the left big toe in 82 patients. Forty-four patienst (26·8 per cent of all patients) had both feet affected at the same time.

Type of operation

A total of 245 operations had been performed on 208 patients, some patients having had both feet treated at the same time.

Table I shows the type of operation performed, total avulsion of the nail being the most common treatment.

Table II shows the recurrence rate for each procedure, the most frequently used operation giving the highest recurrence rate.

There had been a variety of subsequent treatments. Nine of the patients said they had had 3 or more subsequent operations on the same toe, while 10 had had 2 subsequent operations. These procedures were usually avulsion of the nail, although 1 patient had had a total of 4 Zadik operations on the same toe!

Of the 139 patients who had required further treatment, 61·8 per cent had gone to other hospitals for this.

Table I: TYPE AND NUMBER OF OPERATIONS PERFORMED

Type of operation	No.	%
Avulsion of strip of nail	29	12
Total avulsion of nail	131	54
Wedge resection (single and double)	38	15
Total proximal nail bed ablation	47	19

Table II: RECURRENCE RATE FOLLOWING EACH OPERATION

Operation	No.	No. subsequent treatments	Recurrence rate %
Avulsion of strip of nail	29	23	83
Total avulsion of nail	131	92	70
Wedge resection (single and double)	38	11	29
Total proximal nail bed ablation	47	13	28

Discussion

There is little uniformity in the treatment of ingrowing toenails and, all too often, little understanding of the various types of treatment and their complications.

Avulsion of an ingrowing toenail is relatively simple to perform, but this survey demonstrates an unacceptably high recurrence rate of 70 per cent. Murray and Bedi (1978) recorded similar results showing a recurrence rate of 64 per cent after one avulsion and 86 per cent after a second avulsion.

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The reasons for this high recurrence are:

1. When an ingrowing toenail has been present for any length of time, the lateral nail fold becomes large and fibrosed. The new nail is frequently unable to depress this tissue as it regrows, and instead grows into it again.
2. After a nail has been avulsed, the pulp is no longer kept in place and tends to move dorsally. The new nail has to grow over this.
3. The new nail is often thickened and less pliant. As a consequence, it is less able to adapt to any soft tissue it grows against.

Avulsion of a strip of nail has a similar very high recurrence rate and for the same reasons this procedure should not be performed. The aetiological significance of poor foot hygiene, sweaty feet and the wearing of nylon socks is not known, although these factors may contribute to the high recurrence rate.

In this survey, the recurrence rate after both wedge excisions and Zadik operations was just under 30 per cent. This is still high but is similar to the rate reported by Murray and Bedi (1975). Toenail surgery is not easy, great care being necessary to ensure that the nail bed is not completely excised, but all too often the procedure is left to inexperienced doctors who are not adequately trained in the operative techniques. A wedge excision with Steristrip closure is the preferred first line operation.

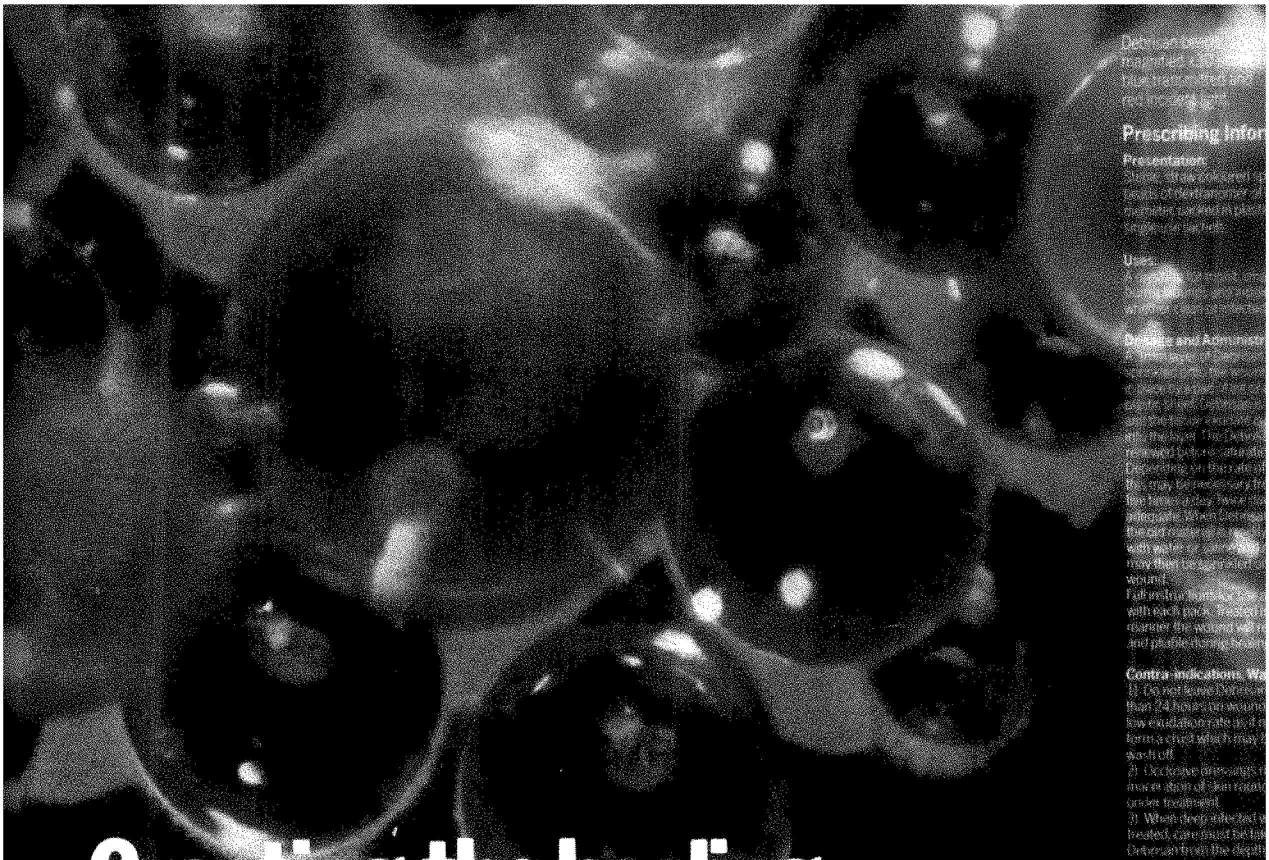
In a toenail clinic at King's College Hospital it is now the policy to treat ingrowing toenails initially with antibiotics, silver nitrate applications and 1/1000 potassium permanganate soaks. Nearly three-quarters of ingrowing toenails improve within 2–3 weeks. In these cases conservative management is continued. If there has been no improvement, a curative operation is performed.

A high percentage of patients changed hospitals for subsequent treatment. Although there is no precise information, a considerable proportion of these patients had had treatment for ingrowing toenails at other hospitals before coming to King's College Hospital. This probably reflects both the lack of efficacy of the treatment and the general lack of interest in the condition shown by doctors.

Reference

MURRAY W. R. and BEDI B. S. (1975) The surgical management of ingrowing toenail. *Br. J. Surg.* **62**, 409.

Paper accepted 26 January 1979.



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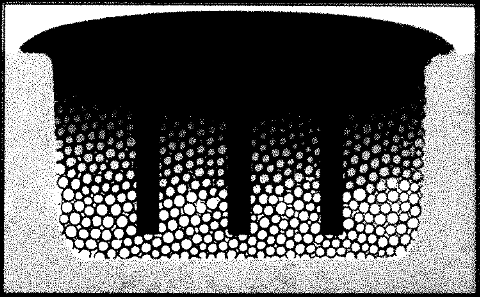

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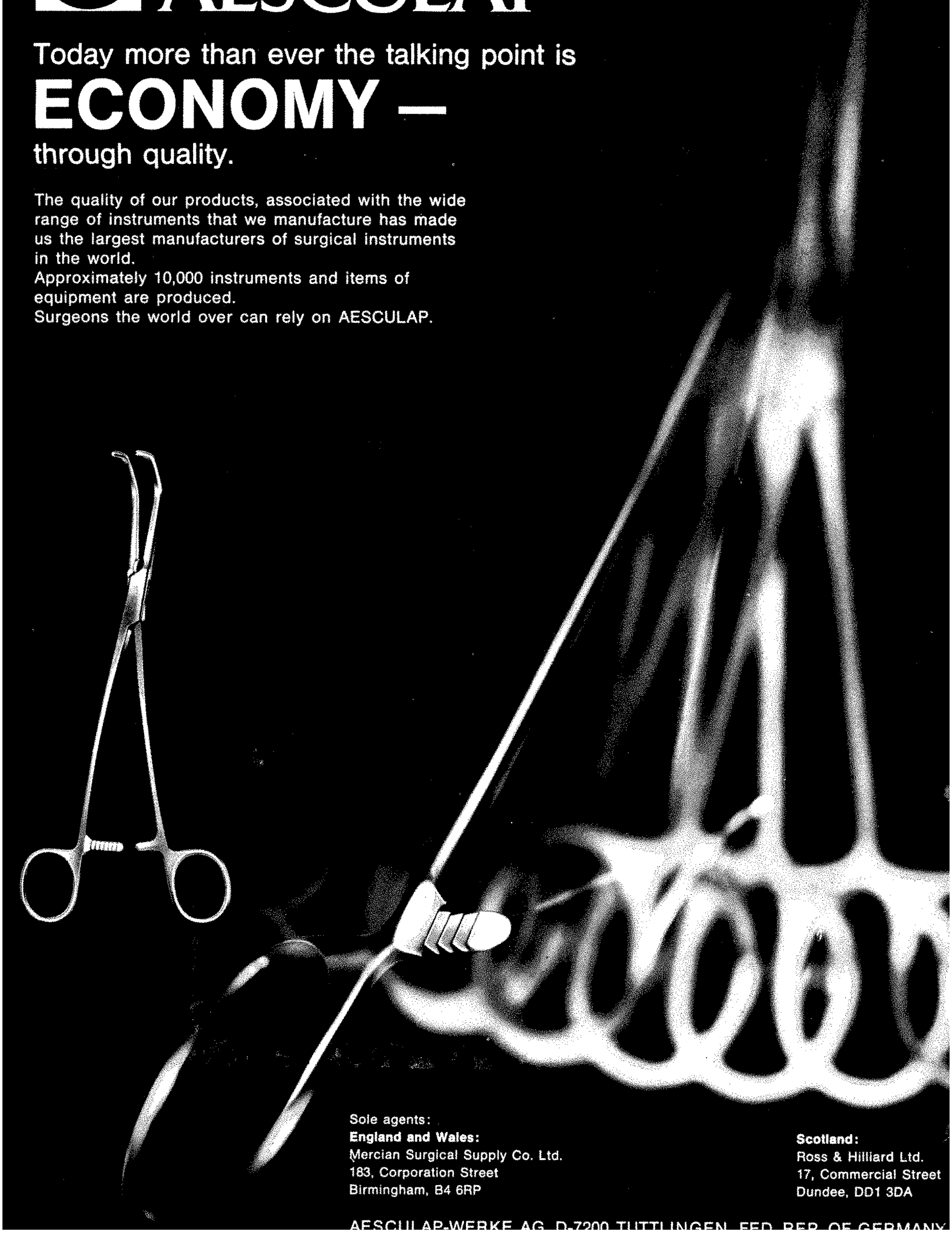

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Br. J. Surg. Vol. 66 (1979) 577–579

Two gas-gangrene-like infections due to *Bacillus cereus*

D. J. FITZPATRICK, P. C. B. TURNBULL, C. T. KEANE AND L. F. ENGLISH*

SUMMARY

Two cases of postoperative gas-gangrene-like infection due to Bacillus cereus are reported, drawing attention to the fact that Bacillus cereus, a common environmental bacterium, can occasionally give rise to severe postoperative infection. Characteristics of the organism related to the epidemiology and pathogenesis of such infections are discussed.

RECENT interest in *Bacillus cereus* has tended to centre on its role as an agent of food poisoning. In fact, the organism has been associated with a wide variety of non-gastrointestinal infections since it was properly established under the name *B. cereus* in 1952 by Smith et al. and, for half a century before that, under various other names such as *B. subtilis, B. anthracoides, B. anthracis similis* and *B. pseudoanthracis* (Gibson and Gordon, 1974).

Apart from a paper in which aerobic spore bearers were mentioned in the context of the bacteriology of air-raid wounds (Spooner, 1941), early published reports of the involvement of these types of bacillus in wound infections have not been found, although they were associated with a wide variety of other types of infection (Turnbull, Jørgensen et al., 1979).

Recently there have been three reports of postoperative gas-gangrene-like infections due to *B. cereus* (Crum, 1976; Groschel et al., 1976; Turnbull, French et al., 1977). Two more cases are presented here, supplying further evidence that this is an organism of which surgical staff should be aware.

Case reports

Case 1: A 45-year-old compositor presented at the outpatient department in June 1977. He complained of pain in the right knee and on examination was found to have neuropathic changes in both knees, with marked valgus deformity and gross instability of the right knee. Amongst various laboratory investigations the treponemal haemagglutination (TPHA) and Khan tests were positive. The patient was diagnosed as having syphilis and penicillin therapy was instituted. The definitive treatment of the right knee was considered to be total joint replacement.

Before admission for this procedure the patient was admitted as an emergency on 1 January 1978 complaining of severe painful swelling of the right lower leg. He was apyrexic and gave no history of trauma other than energetic dancing some 24 h previously. On 2 January the calf was more tense and was decompressed. Postoperatively the patient was initially well, but when the wound was dressed on 6 January it appeared offensive. A Gram stain of the material showed Gram-positive bacilli and, as these were suspected of being a species of clostridium, penicillin therapy was started. Later when culture yielded a pure growth of *B. cereus* sensitive to gentamicin, treatment with this antibiotic was instigated.

The patient's general condition deteriorated and he became increasingly toxic and had a persistent pyrexia. An X-ray of the calf muscles revealed the presence of gas in the tissues. Total débridement of the muscles of the anterior and peroneal compartments was performed. The patient's general state remained unchanged and on 9 January a mid-thigh amputation was performed. Subsequently a wound haematoma was evacuated and the stump healed satisfactorily.

At the initial débridement operation the muscle tissue appeared avascular and bubbles of gas were noted in the deeper muscle separating the individual muscle fibres. Histological examination showed ischaemic necrosis of the muscle with suppuration following infection. Extensive venous thrombosis of the major veins of the leg antedating the onset of symptoms was noted. The appearance of the muscle was not typical of gas gangrene.

A Gram stain of the material showed Gram-positive bacilli and culture yielded *B. cereus.*

The *B. cereus* isolates were submitted to the Food Hygiene Laboratory, Colindale, for confirmation, serotyping and toxin tests.

Case 2: An 18-year-old student was admitted on 19 February 1978 following a road traffic accident. He had sustained bilateral femoral shaft fractures. His peripheral pulses were present but weak. Following resuscitation, the fractures were reduced and he was immobilized on Thomas's splints with skeletal traction.

On 20 February the circulation to the right foot gave cause for concern. A femoral angiogram was performed and occlusion of the femoral artery was noted. The thigh was explored and the fracture plated. The superficial femoral artery and vein were found to have been completely transected, at the level of the adductor tubercle. The artery was repaired utilizing a saphenous vein graft. On 21 February increased calf tension was noted and a further angiogram revealed compression of the anterior tibial vessels. Decompression of the fascial compartments of the leg was carried out.

On 24 February culture from the open leg wound produced a pure growth of *B. cereus*. The patient was grossly toxic with a persistent high temperature in the region of 39·4 °C. He was treated with cephaloridine and streptomycin. Extensive débridement of the anterior and peroneal compartment muscles was performed. At operation ischaemia of the muscle tissue was noticed with gross myonecrosis and possible gas formation deep in the tissues. Histology showed acute inflammation affecting the interstitium of the striated muscle. There was no gross muscle pathology but focal necrosis of the muscle was seen on microscopy. A wound swab taken on 27 February yielded *Pseudomonas aeruginosa* and the patient's treatment was changed to gentamicin. On 28 February a wound swab showed Gram-negative and Gram-positive bacilli and culture yielded *B. cereus* and *Proteus mirabilis*. Also one of a set of four blood cultures grew *Clostridium perfringens* on 26 February. The *B. cereus* isolates were again sent to the Food Hygiene Laboratory.

Cross-infection studies

The patients reported here were admitted to different hospitals but one member of the surgical team had operated on both cases, and initially it was considered that the cases could be related. Nose and throat swabs and hand washings were taken from the relevant personnel on 14 March 1978. *B. cereus* was isolated from the hands of the member of the surgical team common to both cases and the isolates were forwarded to the Food Hygiene Laboratory for cross-matching with the isolates from the two cases.

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Table I: SEROTYPE AND TOXIN PRODUCTION FINDINGS OF *Bacillus cereus* ISOLATES FROM THE 2 CASES AND FROM HAND WASHINGS OF THE MEMBER OF THE SURGICAL TEAM COMMON TO BOTH

Source	Culture date (1978)	Serotype	Intestinal necrosis test*	Skin test* category
Case 1	6 January	2	4+	4^{n}
	7 January	2	4+	5^{n}
	10 January	2	4+	5^{n}
Case 2	24 February	21	±	3
		NT	2+	3^{n}
		NT	2+	2^{n}
	28 February	21	±	2
Surgeon	14 March	NT	—	2
		NT	—	2

* Tests in New Zealand White rabbits.
^{n}, Necrosis developed at the site of injection.
NT, not typable.

Bacteriology and toxicology

In *Case* 1, cultures taken on 6, 7 and 10 January all yielded *B. cereus* serotype 2. An obscure aerobic sporing bacillus, tentatively identified as *B. cirroflagellosus*, was also isolated on 7 and 10 January but the *B. cereus* was reported to have predominated. In the rabbit intestinal necrosis reaction test of Turnbull, Nottingham et al. (1977) and the skin test of Glatz et al. (1974), the *B. cereus* isolates were found to produce high levels of exotoxin (*Table I*). The two tests appear to detect the same toxin which, it has been proposed (Turnbull, 1976; Turnbull, Kramer et al., 1979), is the pyogenic and pyrogenic factor in *B. cereus* infections. The intestinal necrosis test is assessed qualitatively on a 4+ scale while, in the skin test, it has been found (Turnbull, Kramer et al., 1979) that *B. cereus* strains can be conveniently placed into five categories on the basis of the quantitatively measurable zones of reaction. The *B. cirroflagellosus* grew poorly in the growth broth used for toxin testing and could not be assessed toxigenically.

In *Case* 2 cultures taken on 24 February yielded three colonial types of *B. cereus*, a type 21 and two which could not be typed; a type 21 was again isolated on 28 February. All four isolates produced moderate levels of exotoxin (*Table I*) but insofar as they caused greater necrotic reactions in the two test systems, the NT strains were the more toxigenic.

Two apparently distinct *B. cereus* isolates were obtained some days later (14 March) from the hands of the member of the surgical team common to both cases but neither of these could be typed and both were of relatively low toxigenicity (*Table I*). Thus, they could not be related to either of the 2 cases.

Discussion

Some of the clinical features of classic gas gangrene, notably the rapid evolution of the disease, marked disorientation, delirium and prostration (Dineen, 1977), and some pathological features, e.g. spreading oedema (Robb-Smith, 1945), were not manifested in the 2 patients reported here. However, absence of these at the time of initial diagnosis was not sufficient to eliminate the possibility that these were cases of gas gangrene, and it is probable that it would always be necessary to treat this type of case as such at the outset.

In comparing the 2 cases, although many factors may have influenced the clinical features observed, it is probably relevant that the more severe infection in *Case* 1 correlated with the greater toxigenicity of the isolates from that case. In fact, in a study on the production of this toxin by *B. cereus* isolates from 21 cases of a variety of infections (Turnbull, Jørgensen et al., 1979), isolates from our *Case* 1 gave the highest readings obtained.

In *Case* 2 the roles of *P. aeruginosa*, *P. mirabilis* and *C. perfringens* cannot be definitely assessed but the facts that they were each only isolated on a single occasion and that the *C. perfringens* was not isolated from the infection site suggest that they were not of particular consequence. Transient bacteraemia with *C. perfringens* is fairly common (Ahmad and Darrell, 1976; *British Medical Journal*, 1976).

Although serotyping and toxin production results failed to establish an epidemiological relationship between the 2 cases and their 'link', this does not exclusively rule out the possibility that they were associated through this link. On the other hand, it is more likely that the infections were autogenous or were derived during dressing of the wounds. Apart from a study showing a 14 per cent carriage rate in faeces of laboratory staff (Ghosh, 1978), no published reports have been found of carriage of *B. cereus* by healthy persons. However, *Bacillus* as a group have been reported as being the most common species recoverable from the scalp (Roia and Vanderwyk, 1969), and using an adhesive tape strip test, isolation of *B. cereus* from the foreheads of staff of the laboratory of a large London Hospital was recorded as 'not common' (Taylor, 1978). Consistent isolation of *B. cereus* over a 16-week period from the hands of a member of the Food Hygiene Laboratory who worked with the organism, despite careful technique and rigorous handwashing, including a disinfectant rinse (Turnbull, unpublished results), suggests that the organism can survive well on the hands.

Spores of *Bacillus* spp. on moist or dry surfaces are highly resistant to skin disinfectants; studies reviewed by Sykes (1965) showed that sterilizing times with 2 per cent alcoholic iodine or optimal iodophore concentrations ranged from 90 min to many hours. As stressed previously (Turnbull, French et al., 1977), in preparing skin for surgery the importance of careful cleansing with detergent before application of alcoholic iodine or iodophore cannot be overemphasized.

Gas formation within the tissues was reported in one of the previous cases (Groschel et al., 1976). This is of interest in that in routine laboratory tests, *B. cereus*, in contrast to *C. perfringens*, does not produce gas to any obvious extent. However, production of gas during anaerobic reduction of nitrate is a characteristic of *B. cereus* (Smith et al., 1952) and is commensurate with the finding of gas in the tissues.

Although occasional penicillin-sensitive strains are encountered, as a group *B. cereus* organisms are β-lactamase producers. Apparently, most strains are sensitive to gentamicin (Turnbull, Jørgensen et al., 1979), which would be a reasonable choice of therapy.

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References

AHMAD F. J. and DARRELL J. H. (1976) Significance of the isolation of *Clostridium welchii* from routine blood cultures. *J. Clin. Pathol.* **29**, 185–186.

BRITISH MEDICAL JOURNAL (1976) *Clostridium welchii* from blood culture. **1**, 382.

CRUM L. (1976) Gas gangrene-like infection with *Bacillus cereus* in lymphoma patient. Paper presented at an International Conference of Medical Technology, Chicago, 22 June 1976.

DINEEN P. (1977) Gas gangrene. In: HOEPRICH P. D. (ed). *Infectious Diseases*, 2nd ed. Hagerstown, Maryland, Harper & Row, pp. 1152–1155.

GHOSH A. C. (1978) Prevalence of *Bacillus cereus* in the faeces of healthy adults. *J. Hyg. (Camb.)* **80**, 233–236.

GIBSON T. and GORDON R. E. (1974) Genus *Bacillus*; 4. *Bacillus cereus*. In: BUCHANAN R. E. and GIBBONS N. E. (ed.) *Bergey's Manual of Determinative Bacteriology*, 8th ed. Baltimore, Williams & Wilkins, pp. 534–535.

GLATZ B. A., SPIRA W. M. and GOEPFERT J. M. (1974) Alteration of vascular permeability in rabbits by culture filtrates of *Bacillus cereus* and related species. *Appl. Microbiol.* **10**, 229–303.

GROSCHEL D., BURGESS M. and BODEY G. P. (1976) Gas-gangrene-like infection with *Bacillus cereus* in a lymphoma patient. *Cancer* **37**, 988–991.

ROBB-SMITH A. H. T. (1945) Tissue changes induced by *Cl. welchii* type A filtrates. *Lancet* **2**, 362–368.

ROIA F. C. and VANDERWYK R. W. (1969) Resident microbial flora of the human scalp and its relationship to dandruff. *J. Soc. Cosmetic Chem.* **20**, 113–134. (Cited by WOODROFFE R. C. S. and SHAW D. A. (1974) Microbial populations on skin and hair. In: SKINNER F. A. and CARR J. G. (ed.) *The Normal Microbial Flora of Men*. London, Academic Press, p. 14.)

SMITH N. R., GORDON R. E. and CLARKE F. E. (1952) *Aerobic Spore-forming Bacteria*. United States Department of Agriculture, Monograph No. 16, pp. 56–64.

SPOONER E. T. C. (1941) The bacteriology of air-raid wounds examined within forty-eight hours of infliction. *Br. Med. J.* **2**, 477–478.

SYKES G. (1965) *Disinfection and Sterilization*, 2nd ed. London, E. & F. N. Spon, pp. 402–406.

TAYLOR A. J. (1978) Personal communication.

TURNBULL P. C. B. (1976) Studies on the production of enterotoxins by *Bacillus cereus*. *J. Clin. Pathol.* **29**, 941–948.

TURNBULL P. C. B., FRENCH T. A. and DOWSETT E. G. (1977) Severe systemic and pyogenic infections with *Bacillus cereus*. *Br. Med. J.* **1**, 1628–1629.

TURNBULL P. C. B., JØRGENSEN K., KRAMER J. M. et al. (1979) Severe clinical conditions associated with *Bacillus cereus* and the apparent involvement of exotoxins. *J. Clin. Pathol.* **32**. (In the press.)

TURNBULL P. C. B., KRAMER J. M., JØRGENSEN K. et al. (1979) Properties and production characteristics of vomiting, diarrhoeal and necrotizing toxins of *Bacillus cereus*. *Am. J. Clin. Nutr.* **32**. (In the press.)

TURNBULL P. C. B., NOTTINGHAM J. F. and GHOSH A. C. (1977) A severe necrotic enterotoxin produced by certain food, food poisoning and other clinical isolates of *Bacillus cereus*. *Br. J. Exp. Pathol.* **58**, 273–280.

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Wound sepsis following gastrointestinal surgery: a comparison of topical and two-dose systemic cephradine

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SUMMARY

A prospective study of the effect of the route of administration of prophylactic antibiotic on the wound infection rate following gastrointestinal surgery was performed. Patients were randomly allocated to one of three groups: group 1 received no form of antibiotic prophylaxis; group 2 received 1 g of cephradine applied topically to the wound at closure; group 3 received 1 g of cephradine intravenously at induction of anaesthesia and a further intravenous dose of 500 mg 4 h later. Wound infections occurred in 12 of 83 patients in the control group (14·5 per cent), in 6 of the 83 patients in the group who received topical antibiotic (7·2 per cent) and in 3 of the 82 patients who received systemic antibiotics (3·6 per cent). Only the group who received systemic antibiotic showed a statistically significant reduction in the incidence of wound infections compared with the control group ($P = 0.03$).

WOUND infection rates of 9–22 per cent are commonly seen following gastrointestinal surgery, even if patients in whom pus is present at operation are excluded (Cruse and Foord, 1973). Although infection rates can only be reduced to acceptable levels by employing meticulous standards of surgical technique, the additional use of prophylactic antibiotics administered either topically into the wound or systemically during surgery has become increasingly popular in recent years (Keighley, 1977). However the value of such prophylactic regimens is still questioned (Spievack, 1978).

The present study was planned to examine the effect of the broad spectrum antibiotic cephradine on the incidence of postoperative wound infection after gastrointestinal surgery, and to compare the effect of topical administration of the antibiotic with systemic administration of the same antibiotic.

Patients and methods

Patients admitted to the Nuffield Department of Surgery for gastrointestinal surgery (both elective and emergency) during the 11-month period from August 1977 to July 1978 were entered into the trial. Immediately before surgery, patients were allocated to one of the three arms of the trial by opening sealed envelopes containing previously randomized cards: group 1, control group—no antibiotic treatment; group 2, topical antibiotic—1 g cephradine administered topically into the wound at the time of closure; group 3, systemic antibiotic—1 g cephradine administered intravenously at the time of induction of anaesthesia and 500 mg administered intravenously 4 h later.

For the duration of the trial all wounds were closed with continuous nylon sutures with the exception of muscle-splitting incisions which were closed with chromic catgut. Wounds were not drained unless the subcutaneous fat exceeded 2·5 cm and all peritoneal drains were brought out through separate incisions. Bowel preparation before colonic surgery was by mechanical means only.

Wounds were inspected daily from the fourth postoperative day by a research nurse who was unaware of the group into which the patient had been allocated. Wound sepsis was defined as the presence of pus in a wound which spontaneously discharged or had to be released by removing sutures and opening the incision (National Research Council, 1964). Swabs were taken from infected wounds by the research nurse and delivered immediately in Stuart's medium to the laboratory for both aerobic culture on blood agar and MacConkey's medium and anaerobic culture on blood agar with 100 μg/ml of neomycin sulphate. Those patients discharged from hospital with their sutures still in place were supplied with a form to be completed by the doctor or nurse at the time of suture removal. Evidence of wound infection was also sought at the routine follow-up clinic 4–6 weeks later.

Subsequently excluded from the trial were all patients who were found at operation to have a bacterial peritonitis secondary to perforation of the small bowel, appendix or colon. Such patients were classified as having 'contaminated' rather than 'potentially contaminated' wounds (Pollock, 1976) and further therapeutic measures were left to the discretion of the surgeon. Also excluded from the trial were all patients who received additional antibiotics within 24 h of surgery, for whatever cause.

Results were analysed for statistical significance by the use of χ^2 test with Yates's correction.

Results

Exclusions (Table I)

Two hundred and eighty patients were originally entered into the trial. At operation 26 patients were found to have a bacterial peritonitis and were subsequently excluded (23 patients with perforation of the appendix, 2 patients with perforation of the small bowel and 1 patient with a colonic perforation). Six of the remaining patients received additional antibiotics either at operation or within 24 h and were also excluded. Three of these patients had salpingitis and normal appendices were removed, 1 patient with carcinoma of the colon had a urinary tract infection and 1 patient underwent abdominoperineal excision of the rectum and total cystectomy with gross faecal soiling of the abdominal cavity. The final patient underwent a prolonged operation on the biliary tract. In the last two patients the surgeon involved felt that a full course of antibiotics was indicated.

Distribution of uncontrolled variables

There was an even distribution between the three groups with respect to age of the patients, experience of the surgeon and acute or elective nature of the operation. Wound drains were employed in a total of 8 patients (4 patients in the control group, 1 in the group that received topical antibiotic and 3 in the group that received systemic antibiotic).

Wound infections (Table II)

Twelve wound infections (14·5 per cent) occurred in the control group of 83 patients who received no antibiotic at the time of operation. Six wound infections were recorded in the group of 83 patients who received topical antibiotic (7·2 per cent) but this result did not differ significantly from that recorded in the control group ($\chi^2 = 1·56$, $P > 0·05$). Three wound infections occurred in the group of 82 patients who received systemic antibiotic (3·6 per cent) and the difference between this figure and that recorded in the control group was significant ($\chi^2 = 4·59$, $P = 0·03$). In this group the three infections followed appendicectomy in two patients (one normal and one gangrenous) and a left hemicolectomy for carcinoma in a third patient. However, the difference between the infection rates in the two groups receiving antibiotic prophylaxis was not significant ($\chi^2 = 0·04$, $P > 0·05$).

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Bacteriology (*Table III*)

Table III summarizes the organisms isolated from the 21 infected wounds in this series. *Staphylococcus aureus* was isolated from 7 wounds in the control group but from none of the wounds in the two treated groups. *Clostridium welchii* was isolated from 2 of the patients in the control group and from 1 patient who received topical antibiotic. One of the patients in the control group developed clinical gas gangrene of the wound and subsequently died. *Bacteroides fragilis* was isolated from a total of 6 wounds; 3 in the control group, 2 in the topical antibiotic group and 1 in the systemic antibiotic group.

Other septic complications (*Table IV*)

Fifteen patients in the control group developed other significant infective complications after surgery. Ten patients developed chest infections and 5 patients developed infections of the urinary tract. In the group receiving topical antibiotic, 13 infective complications were recorded, including 2 patients who each developed a pelvic abscess. In the group who received systemic cephradine only 6 such complications occurred (this was not significantly different from that recorded in the control group, $\chi^2 = 3·7$, $0·05 < P < 0·1$).

Discussion

These results show that a significant reduction in the wound infection rate following gastrointestinal surgery can be achieved by the systemic administration of two doses of the broad spectrum antibiotic cephradine at the time of surgery. This two-dose regimen is designed to give a maximum tissue concentration of antibiotic at the time of contamination and is based on the classic experimental studies of Burke (1961). He demonstrated in the guinea-pig that a single intravenous dose of antibiotic given at, or just before, intradermal inoculation of bacteria was the most effective method of preventing the development of infected lesions and that the antibiotic was completely ineffective if given more than 3 h after inoculation. This regimen does not favour the emergence of antibiotic-resistant strains of bacteria provided a bactericidal drug is used. Cephradine was selected for use in this trial because of its broad spectrum of activity which includes *Staphylococcus aureus* and most of the common bowel pathogens. It has been shown to have a high resistance to β-lactamases (Selwyn, 1976) and has activity against some anaerobic bacteria including some *Bacteroides* species (Shadomy et al., 1977).

Table I: PATIENTS EXCLUDED FROM THE TRIAL

	Control	Topical cephradine	Systemic cephradine
Perforated viscus*	8	8	10
Antibiotics within 24 h of operation	1	2	3

* Not including gastric and duodenal perforations.

Table II: WOUND INFECTION RATE IN THREE GROUPS SUBDIVIDED ACCORDING TO THE SITE OF OPERATION

	Control		Topical cephradine		Systemic cephradine	
	I	NI	I	NI	I	NI
Gastric	2	8	1	8	0	9
Biliary	2	12	0	8	0	12
Small bowel	2	2	0	0	0	1
Appendix	3	44	1	51	2	44
Colorectal	3	5	4	10	1	13
	12	71	6	77	3	79

I, Infected; NI, not infected.
Control *v.* topical, $\chi^2 = 1·56$, $P =$ N.S.
Control *v.* systemic, $\chi^2 = 4·59$, $P = 0·03$.

Table III: ORGANISMS CULTURED FROM INFECTED WOUNDS IN EACH OF THE THREE GROUPS

	Control	Topical cephradine	Systemic cephradine
Staphylococcus aureus	7	0	0
Escherichia coli	2	2	2
Proteus spp.	2	0	0
Streptococcus faecalis	2	2	2
Haemolytic streptococcus	2	0	0
Klebsiella spp.	0	1	0
Clostridium welchii	2	1	0
Bacteroides fragilis	3	2	1

Table IV: OTHER INFECTIVE COMPLICATIONS IN EACH OF THE THREE GROUPS

	Control	Topical cephradine	Systemic cephradine
Chest infection	10	6	4
Urinary tract infection	5	5	2
Pelvic abscess	0	2	0
Total	15	13	6

Control *v.* systemic, $\chi^2 = 3·7$, $0·05 < P < 0·1$.

These results further suggest that the use of systemic antibiotic prophylaxis is more effective than the topical application of the antibiotic at the end of the operation. In view of the experiments of Burke (1961) this is not surprising, as the antibiotic is being added to the wound after contamination has occurred. Although topical cephradine failed to reduce significantly the wound infection rate, a larger trial would have been necessary to have demonstrated a statistically significant difference between this group and the group that received systemic antibiotic.

A further disadvantage of topical antibiotics has been noted by Keighley (1977), namely that they are unlikely to affect the incidence of infective complications outside the wound. Our data would support this suggestion. In this series the incidence of such complications in the group receiving topical antibiotic was very similar to that seen in the control group. In the group receiving systemic antibiotic, the incidence of such complications was reduced from 15 to 6 per cent, but these figures just failed to reach the level of significance.

The infection rate of 14·5 per cent recorded in the untreated control group in this study is relevant to the discussion. Spievak (1978), in his editorial 'The prophylactic antibiotic puzzle', has pointed out that a significant reduction in the wound infection rate in most published series has only been recorded when the infection rate in the control group is in the range of 20–60 per cent, a figure that he considers unacceptably high. Inspection of the infection rates quoted by Keighley (1977) in his recent review lends support to this argument. All 18 of the published series cited in which the infection rate in the control group exceeded that reported in this series showed a significant reduction in infection rates in the antibiotic-treated groups. However, in only 3 of the 8 series cited in which the control infection rate was lower than that reported here was this infection rate lowered by prophylactic antibiotics. The infection of 14·5 per cent reported here, whilst failing to meet the figure of 5 per cent demanded by Spievak in clean cases, is entirely acceptable in our opinion as this study included only patients with 'potentially contaminated' wounds. Furthermore, the majority of operations were performed as emergency procedures by surgeons below the grade of consultant.

Burdon et al. (1978) have reported recently the failure of systemic cephalothin given at surgery to reduce significantly the wound infection rate following colonic surgery. This may have been due to low resistance of cephalothin to β-lactamase compared with cephadine, and to cephalothin's greater affinity for protein binding resulting in lower tissue levels of free antibiotic (Selwyn, 1976). In the present series the most noticeable reduction in wound sepsis appeared to occur amongst the patients who underwent colorectal surgery. Only 1 wound infection occurred in the 14 patients who received systemic cephradine compared with 4 infections in the 14 who received topical antibiotic and 3 infections in the 8 patients in the control group. However, the numbers in these groups are too small to reach statistical significance.

In view of the recent interest shown in evaluating the importance of anaerobic organisms in the pathogenesis of wound sepsis, particular attention was paid in this trial to the collection of material for anaerobic culture (Kelly and Warren, 1978). *Bacteroides fragilis* was isolated from 6 of the 21 infected wounds in this series (29 per cent), a similar figure to that recently reported by Pollock et al. (1978). However, *Bacteroides fragilis* alone was cultured from only one of the infected wounds in the group that received systemic antibiotic and from two of the wounds in the group that received topical prophylaxis. It is thus doubtful whether the additional prophylactic administration of an agent active only against anaerobic organisms would confer any significant advantage in patients undergoing potentially contaminated gastrointestinal surgery over the use of a single broad spectrum antibiotic such as cephradine, whose range of clinical activity includes some of the anaerobic pathogenic bacteria (Shadomy et al., 1977).

Conclusions

A simple two-dose course of systemic cephradine given at the time of surgery can reduce the wound infection rate following gastrointestinal surgery to a level of 3·5 per cent even when the infection rate in patients not receiving antibiotic prophylaxis is as low as 14·5 per cent. This regimen appears more effective than the topical application of antibiotic into the wound which did not significantly reduce the postoperative infection rate. It is unlikely that any significant further improvement would be obtained by the addition of an agent specifically active against anaerobic organisms.

References

BURDON J. G. W., MORRIS P. J., HUNT P. et al. (1978) A trial of cephalothin sodium in colon surgery to prevent wound infection. *Arch. Surg.* **112**, 1169–1173.

BURKE J. F. (1961) The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery* **50**, 161–168.

CRUSE P. J. E. and FOORD R. (1973) A five-year prospective study of 23,469 wounds. *Arch. Surg.* **107**, 206–210.

KEIGHLEY M. R. B. (1977) Prevention of wound sepsis in gastrointestinal surgery. *Br. J. Surg.* **64**, 315–321.

KELLY M. J. and WARREN R. E. (1978) The value of an operative wound swab sent in transport medium in the prediction of later clinical wound infection: a controlled clinical and bacteriological evaluation. *Br. J. Surg.* **65**, 81–88.

NATIONAL RESEARCH COUNCIL (1964) Report of an Ad Hoc Committee of the Committee on Trauma, Division of Medical Sciences, Natural Academy of Sciences: National Research Council: Postoperative Wound Infections. *Ann. Surg.* **160**, Suppl. 1, pp. 1–192.

POLLOCK A. V. (1976) In: Topical chemoprophylaxis in surgery. WILLIAMS J. D. and GEDDES A. M. *Chemotherapy*, 3rd ed. New York, Plenum Press, p. 342.

POLLOCK A. V., FROOME K. and EVANS M. (1978) The bacteriology of primary wound sepsis in potentially contaminated abdominal operations: the effect of irrigation, povidone-iodine and cephaloridine on the sepsis rate assessed in a clinical trial. *Br. J. Surg.* **65**, 76–80.

SPIEVACK A. R. (1978) The prophylactic antibiotic puzzle. *Surg. Gynecol. Obstet.* **147**, 80.

SELWYN S. (1976) Rational choice of penicillins and cephalosporins based in parallel *in-vitro* and *in-vivo* tests. *Lancet* **2**, 616–619.

SHADOMY S., MAYHALL C. G. and APOLLO E. (1977) *In vitro* activity of five oral cephalosporins against anaerobic pathogenic bacteria. *J. Infect. Dis.* **136**, 697–700.

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Leucocyte ascorbate levels and postoperative deep venous thrombosis

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SUMMARY

Forty-four general surgical patients were included in a prospective, randomized double-blind controlled trial of ascorbic acid (500 mg b.d.) or placebo for 7 days before operation. This was to test the hypothesis that vitamin C may reduce the instance of deep venous thrombosis postoperatively. Venous blood samples were taken before entering the trial, just immediately before surgery, on the day of operation and on three further occasions at 3-day intervals postoperatively for leucocyte ascorbic acid concentration (LAC). Venous thrombosis was diagnosed using the ^{125}*I-fibrinogen test and the leg scans interpreted by Roberts' criteria. There was no significant difference in the incidence of DVT between the treatment and placebo groups. In those with DVT* (n = *23) the mean LAC on the day of operation was not significantly different from that in those without DVT. However, on the sixth and ninth postoperative days LAC levels were significantly lower in the DVT group. These results suggest that the administration of ascorbic acid preoperatively does not reduce the incidence of DVT, but a striking decrease in the LAC levels in the DVT patients is in keeping with the hypothesis that the initial event in the pathogenesis of DVT is adherence of leucocytes to the venous endothelium.*

It is claimed that in the United Kingdom approximately 21 000 patients die each year from pulmonary embolism (DHSS, 1970) and, while the case for prophylaxis for deep venous thrombosis has recently been reviewed (Kakkar, 1977), considerable controversy exists as to the best methods. Currently available methods are aimed at preventing deep venous thrombosis by elimination of stasis in the deep veins and by counteracting changes in blood coagulability. Low dose subcutaneous heparin is widely used (Kakkar et al., 1975) but excessive blood loss during and after operation, thrice daily injections and, perhaps less significantly but important none the less, the economic implications of this therapy have all restricted its use. Spittle (1973), believing that vitamin C is necessary for the provision and maintenance of a healthy ground substance of blood vessel walls, suggested a role for vitamin C therapy as a prophylactic against postoperative deep venous thrombosis and provided data to support her view. Andrews and Wilson (1973), using a much smaller dose of vitamin C, could not confirm Spittle's report. Should vitamin C be effective then its well-known freedom from side effects, ease of administration and low cost would make it an attractive alternative in clinical practice. The question of the usefulness of vitamin C in preventing deep venous thrombosis remained open and clearly required further study.

Patients and methods

A prospective randomized double-blind controlled trial has been carried out in 43 general surgical patients allocated to either vitamin C 500 mg twice daily or placebo tablets twice daily. Treatment commenced 7 days before and stopped on the day immediately before surgery. Samples of venous blood for leucocyte ascorbate estimations by the method of Denson and Bowers (1961) were taken before treatment, again on the day of operation and on three further occasions postoperatively at 3-day intervals. Venous thrombosis was diagnosed by the ^{125}I-fibrinogen test using the criteria of Roberts (1975).

Patients were scanned preoperatively and then daily for at least 7 days. Special importance was attached to analysis of the results by the method of Roberts in an attempt to overcome inaccuracies produced by variations in background radioactivity, possible misplacement over the precordium and by variations in blood volume in the lower limb produced by vasoconstriction or dilatation. Leg counts were referred to the 'preoperative baseline' rather than to counts made immediately after operation (Kakkar et al., 1970). All data, including recordings of weight, age, initial haemoglobin, haematocrit, presence or absence of malignancy, premedication drugs, details of intravenous fluids, smoking history, day of postoperative mobilization, thrombus score (number of elevated points on limb × the number of days the point was elevated) and the leucocyte ascorbate concentration (LAC), were transferred to punch cards before processing on a CDC 7600 computer. Patients excluded were those over the age of 70 years and, for technical reasons, those undergoing varicose vein or reconstructive peripheral arterial surgery. Twenty patients received ascorbic acid and 23 placebo. The treatment and placebo groups were not significantly different from each other initially (*Table I*). All probabilities shown are two-tailed, except where otherwise stated.

Results

The treatment and placebo groups had a significantly different mean LAC on the day of operation (P = 0·001) (*Table II*) and these differences remained up to the sixth postoperative day. By the ninth day there was no significant difference in leucocyte ascorbic levels between the two groups. In the treatment group 9 of 20 patients, and in the placebo group 13 of 23, developed deep venous thrombosis as detected by the ^{125}I-fibrinogen test. This difference is not statistically significant (corrected χ^2 = 0·2, d.f. = 1, P = 0·65, *Table III*). These findings are in conflict with those of Spittle (1973) but in agreement with those of Andrews and Wilson (1973). A thrombus score was formulated comprising the sum of the number of days on which the radioactivity at each point was elevated and again there were no significant differences between the two groups using the Mann–Whitney U test on the thrombus score (*Table IV*).

There was a marked postoperative reduction by day 3 in the leucocyte ascorbate concentration; the reduction was similar in magnitude in both the ascorbic acid and placebo groups, each showing an

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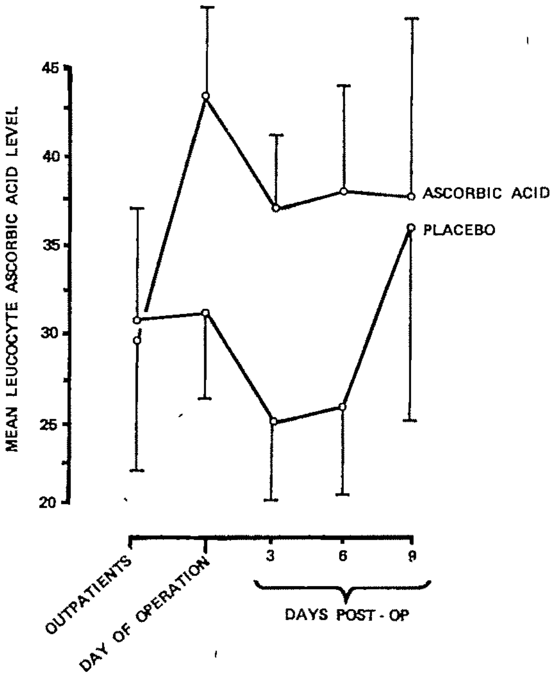

Fig. 1. Postoperative time course of mean leucocyte ascorbic acid levels in treatment and placebo group (95% confidence limits for each mean are shown).

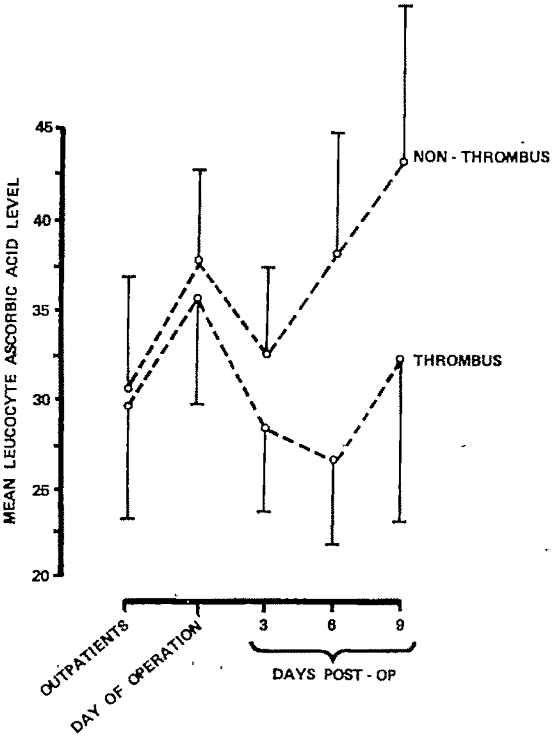

Fig. 2. Postoperative patterns of leucocyte ascorbic acid levels in the thrombus and non-thrombus group (95% confidence limits for each mean are shown).

Table I: COMPARISON OF ASCORBIC ACID AND PLACEBO GROUPS

	t*	P
Age	0·44	0·33
Haemoglobin	1·02	0·16
PCV	−0 86	0·39
Weight	1·24	0·22
	Corrected χ^2†	P
Sex	0·167	0·68
Malignancy	1·25	0·26
Premedication	2·95	0·09
i.v. fluids	0·20	0·65
	Mann–Whitney U test z‡	P
Smoking	−0·112	0·91
WCC	−0·037	0·97
Day of mobilization	−0 853	0·39

* d.f. = 41.
† d.f. = 1.
‡ $z = (U - \mu_u)/\sigma_u$ and is approximately distributed as a standard normal deviate.
PCV, Packed cell volume; WCC, white cell count.

Table II: LEUCOCYTE ASCORBIC ACID: COMPARISON OF ASCORBIC ACID AND PLACEBO GROUPS

LAC at:	t	d.f.	P*
Outpatients	−0·39	41	0·35
Day of operation	3·51	41	0·001
Day 3	4 43	41	0·001
Day 6	3 48	36	0·001
Day 9	0·26	17	0·4

* One-tail probabilities.

Table III: OCCURRENCE OF THROMBUS IN ASCORBIC ACID AND PLACEBO GROUPS

	Ascorbic acid	Placebo
Non-thrombus	11	10
Thrombus	9	13

Corrected $\chi^2 = 0{\cdot}2007$; d.f. = 1; $P = 0{\cdot}654$.

Table IV: COMPARISON OF THROMBUS SCORES IN ASCORBIC ACID AND PLACEBO GROUPS

	Thrombus score*	
Treatment group	Median	95% confidence limits†
Ascorbic acid ($n = 20$)	2	0–8
Placebo ($n = 23$)	3·5	0–12

* Mann–Whitney U test for difference between groups: $z = -0{\cdot}168$, $P = 0{\cdot}87$ (z is calculated as for *Table I*).
† The approximate 95% confidence limits are for the population median.

almost parallel decrease in the levels (*Fig.* 1). In the placebo group the LAC rose gradually between the third and sixth postoperative days and then sharply between the sixth and ninth, bringing the level up almost to that in the patients treated with ascorbic acid. Considering our patients as thrombus and non-thrombus groups irrespective of whether they received ascorbic acid or not, analysis has revealed an interesting trend (*Fig.* 2). Leucocyte ascorbate curves show separation occurring from the day of operation. Between day 3 and day 6 the curves move in opposite directions, a marked increase occurring in the non-thrombus group but clearly a decrease in those who develop venous thrombosis. There was no difference between the LAC levels in the thrombus and non-thrombus groups at the initial outpatient assessment and on the day of operation. The decrease in LAC levels at the third postoperative day became statistically significant by days 6 and 9 postoperatively (*Fig.* 2). This suggests that the presence of thrombus may actively reduce the LAC.

The thrombus score was found to be significantly correlated with smoking, preoperative haemoglobin concentration, the LAC level on the sixth postoperative day and the patient's weight (*Table V*). There was a negative correlation with smoking habits ($P = 0{\cdot}007$). The more cigarettes smoked, the smaller was the thrombus score for the patient who developed a positive ^{125}I-fibrinogen scan. There was no significant correlation of thrombus score with age, sex, intravenous fluid regimen and, surprisingly, with the day of mobilization after operation.

Discussion

It is of interest that leucocyte ascorbate levels became significantly lower postoperatively in patients developing venous thrombosis. LAC may possibly act as a monitor of the thrombotic process. This hypothesis accords with the observations of Cooke and his colleagues (1977), who found that thigh vein thrombi were invariably attached to at least one point of the venous wall even as early as the first postoperative day. It is known that endothelial damage, whether surgically induced or not, is soon followed by leucocyte adhesion and invasion of the vein wall (Stewart et al., 1978). The mechanism of reduction in LAC in our study may be related to the size and degree of propagation of the thombus.

It could also be argued that low LAC levels in our thrombosis group indicate a failure of the prescribed dose of the vitamin C to maintain LAC levels and that if larger doses had been given then the postoperative fall in LAC may not have occurred and possibly the outcome as far as thrombosis is concerned would have been different. We have not, however, examined different doses in the present paper and there is scope for further work in this regard.

Smoking, haemoglobin concentration, LAC at 6 days postoperatively and weight are all significantly correlated with the thrombus score (*Table* V). Current theories of the aetiology of deep venous thrombosis have been well summarized recently (Morris and Mitchell, 1977) but curiously this and other authoritative reviews (Kakkar, 1977) have failed to comment on the role of cigarette smoking. Our findings surprisingly indicated that venous thrombosis was less likely and, when it occurred, less severe in those who smoked ($P = 0{\cdot}007$). Similarly, Handle and Teather (1969) noted in patients after myocardial infarction that non-smokers had a significantly higher incidence of deep vein thrombosis than cigarette smokers, a result confirmed independently by Marks and Emerson (1974). In a further study Emerson and Marks (1977) found, again after myocardial infarction, that leg vein thrombosis developed in 12 (50 per cent) of 24 patients who did not smoke cigarettes and in only 2 (13 per cent) of 17 patients who were cigarette smokers. An independent study also using the ^{125}I-fibrinogen test in patients after major surgery compared the incidence of DVT in cigarette smokers and pipe smokers with that in non-smokers, emphasizing that it appeared to be cigarette smoking rather than pipe smoking which 'protected' (Pollock, 1978). It appears that cigarette smoking seems to be almost as effective in preventing leg vein thrombosis as low dose heparin (Emerson and Marks, 1977).

Table V: CORRELATION OF VARIABLE WITH THROMBUS SCORE

Variable	Spearman's rank correlation coefficient	P
Smoking	−0·449	0·007
Haemoglobin	0·3116	0·047
LAC 6 days	−0·303	0·05
Weight	0·357	0·03

Interpretation of these data is difficult and further study appears justified, perhaps using the approach of Clayton et al. (1976), employing relatively easily obtainable data such as smoking habits, age, weight, presence of varicose veins and euglobulin clot lysis time in a logistic discrimination analysis aimed at acceptable preoperative prediction of postoperative venous thrombosis.

References

ANDREWS C. T. and WILSON T. S. (1973) Vitamin C and thrombotic episodes. *Lancet* **2**, 39.

CLAYTON J. K., ANDERSON J. A. and MCNICOL G. P. (1976) Preoperative prediction of postoperative deep vein thrombosis. *Br. Med. J.* **2**, 910–912.

COOKE E. D., LLOYD M. J., BOWCOCK S. A. et al. (1977) Intravenous lignocaine in prevention of deep venous thrombosis after elective hip surgery. *Lancet* **2**, 797–799.

DENSON K. W. and BOWERS E. F. (1961) The determination of ascorbic acid in white blood cells: a comparison of WBC, ascorbic acid and phenolic acid excretion in elderly patients. *Clin. Sci.* **21**, 157–162.

DHSS (1970) Annual Report of Chief Medical Officer of DHSS. London, HMSO.

EMERSON P. A. and MARKS P. (1977) Preventing thromboembolism after myocardial infarction: effect of low dose heparin *v.* smoking. *Br. Med. J.* **1**, 18–20.

HANDLEY A. J. and TEATHER D. (1969) Influence of smoking on deep vein thrombosis. *Br. Med. J.* **2**, 651.

KAKKAR V. V. (1977) The prevention of acute pulmonary embolism. *Br. J. Hosp. Med.* **18**, 32–40.

KAKKAR V. V. et al. (INTERNATIONAL MULTICENTRE TRIAL) (1975) Prevention of fatal postoperative pulmonary embolism by low dose heparin: an international multicentre trial. *Lancet* **2**, 45–51.

KAKKAR V. V., NICOLAIDES A. W., RENNEY J. T. et al. (1970) I-labelled fibrinogen test adapted for routine screening for deep vein thrombosis. *Lancet* **1**, 540–542.

MARKS P. and EMERSON P. A. (1974) Increased incidence of deep vein thrombosis after myocardial infarction in non-smokers. *Br. Med. J.* **3**, 232–234.

MORRIS G. K. and MITCHELL J. R. A. (1977) The aetiology of acute pulmonary embolism and the identification of high risk groups. *Br. J. Hosp. Med.* **18**, 6–12.

POLLOCK A. (1978) Cigarette smoking and postoperative deep vein thrombosis (Letter to the Editor). *Br. Med. J.* **2**, 637.

ROBERTS V. C. (1975) Fibrinogen uptake scanning for diagnosis of deep vein thrombosis: a plea for standardisation. *Br. Med. J.* **3**, 455–458.

SPITTLE C. R. (1973) Vitamin C and deep vein thrombosis. *Lancet* **2**, 199–201.

STEWART G. J., LYNCH P. R., REICHLE F. A. et al. (1978) The adhesion of leucocytes, erythrocytes and noncellular material to the luminal surface of natural and artificial blood vessels *in vivo. Ann. NY Acad. Sci.* **283**, 179–207.

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Leg haemodynamics during reconstructive vascular surgery

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SUMMARY

The aim of this study was to find the best haemodynamic variables for a correct assessment of the function of a femoropopliteal bypass graft. The results are based on intraoperative measurements performed on 11 patients undergoing surgical reconstruction of the femoral artery with a femoropopliteal reversed saphenous vein bypass graft.

Both blood transfusion and local intra-arterial injection of 40 mg of papaverine resulted in a significant increase in common femoral arterial and graft blood flows as well as in femoropopliteal pressure difference. At the same time there was a significant decrease in total leg and lower leg resistance, whereas the resistance over the graft was not significantly altered by changes in blood volume or by pharmacological vasodilatation.

It was shown that, for a complete assessment of the bypass function, both the resistance in the graft and in the lower leg must be evaluated. This can be effected by simultaneously measuring both the blood pressure and the blood flow. It was also shown that the femoropopliteal pressure difference per se does not indicate the true capacity of the graft. It is concluded that, during reconstructive vascular surgery, leg haemodynamic variables are influenced by variations in blood volume and vasomotor tone. This is of importance for the correct interpretation of a single haemodynamic variable and for the correct quantitative evaluation of the results of vascular surgery.

THE aim of vascular reconstructive surgery is to restore an adequate blood flow, and the immediate effect of a successful operation is an increased blood flow through the reconstructed vessel and a reduced pressure gradient across it. For the intraoperative evaluation of the results of the reconstructive procedure, most vascular surgeons rely upon flow measurements only, which is sufficient in most cases. Misleading conclusions can be drawn, however, if these measurements are based on either pressure recordings or flow measurements alone, as these two variables depend on each other. Furthermore, there are great variations during surgery in the intravascular volume and, consequently, in peripheral vascular resistance, which both influence blood flow.

The aim of this investigation was to study how, during reconstructive vascular surgery, the peripheral vascular resistance and, consequently, the blood flow in the legs are influenced by changes in intravascular volume and by pharmacological vasodilatation with papaverine, a drug frequently used to estimate flow capacity in reconstructed segments (Cappelen and Hall 1964; Dedichen, 1973).

Patients and methods

Patients

Eleven male patients with a mean age of 58 years (range 47–71) were studied during reconstruction with a femoropopliteal reversed saphenous vein bypass graft. They were all operated on because of symptomatic atherosclerotic occlusion of the superficial femoral artery. The indications for surgery were intermittent claudication in 10 patients and rest pain in 1 patient. None of the patients suffered from gangrene. Two had diabetes mellitus. All the patients underwent preoperative arteriography to determine the extent of arterial occlusion and the degree of atherosclerotic involvement of the popliteal artery and its three branches. Outflow in the lower leg arteries was graded according to Hall (1964) as good (grade A) when all the three lower leg arteries were open with fairly good calibres and even contours (10 patients) and as bad (grade B) in the remaining 1 patient.

Preoperative examinations included chest X-ray, an exercise test with ECG recordings and spirometry. Five patients showed moderate ECG changes during exercise, indicating ischaemic heart disease, and 1 patient showed signs of obstructive pulmonary disease.

The patients were fully informed of the objective and procedure of the study before their free consent to participate was obtained. The protocol was reviewed and approved by the ethical committee of the Karolinska Institute at Huddinge Hospital.

Methods

The patients were premedicated with 5–7·5 mg of droperidol (Dridol), 5–10 mg of diazepam (Valium) and 0·5 mg of atropine intramuscularly. Anaesthesia was induced by 5–10 mg of droperidol, 0·3–0·5 mg of fentanyl (Leptanal) and 5–8 mg of pancuronium bromide (Pavulon). The patients were ventilated mechanically with nitrous-oxide–oxygen (2 : 1) through an Engström ventilator (model 300) with minute volumes set according to the nomogram of Engström and Herzog (1959). An even depth of anaesthesia was maintained by additional doses of fentanyl (0·1–0·3 mg/h) and pancuronium bromide (0·1–1·8 mg/h).

The reconstruction with a femoropopliteal saphenous vein bypass graft was performed without blood transfusion. After completion of the reconstructive procedure, measurements of blood flows and recordings of blood pressures were performed before and during vasodilatation, induced by injecting 40 mg of papaverine into the common femoral artery. Flow measurement and pressure recordings were performed simultaneously and were followed by transfusion of 900 ml of warmed blood (37 °C). After 5–10 min, when a steady state was reached, the measurements were repeated before and during vasodilatation.

Flow measurements: Blood flows in the vein bypass graft and common femoral artery were measured with a square-wave electromagnetic flowmeter (Nycotron, model 376, Norway) (Cappelen and Hall, 1967). The calibration factors for the probes given by the manufacturer were used. Zero flow references were obtained by mechanical occlusion of the vessels (Schenk and Dedichen, 1967).

Pressure measurements: In 8 patients a Teflon catheter (outer diameter 1·2 mm) was inserted percutaneously into the brachial artery and advanced to the subclavian artery. In all 11 patients 2 similar Teflon catheters were inserted into the bypass vein through tributaries and advanced to the common femoral artery proximal to the upper anastomosis and to the popliteal artery distal to the lower anastomosis, respectively.

Pressure recordings were performed with pressure transducers of the variable capacitance type (EMT 34, Siemens-Elema AB, Sweden) with the mean pressures obtained by electrical damping. The vertical midpoint between the sternal bone at the 4th intercostal space and the back was used as a zero reference level.

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Calculation of peripheral resistance: Peripheral resistance values for the whole leg and the lower leg were calculated from the pressure and flow values registered in the common femoral and popliteal arteries respectively. The resistance over the bypass graft was calculated by dividing the difference between the pressure in the common femoral and popliteal arteries by bypass flow. The resistance values are given in peripheral resistance units (PRU).

The ECG was monitored continuously and recorded on a Mingograph 61 (Siemens-Elema AB) as well as the signals from the flowmeter and the pressure transducers.

The total blood loss before transfusion was calculated from volume measurements in the suction apparatus and from drapes and swabs: the average was 550 ml (range 350-700). Thus, the patients were deliberately marginally overtransfused with blood (350 ml on average) to offset early postoperative haemorrhage (Hoye et al., 1961).

Statistics: Data in the text and figures are given as mean ± standard deviation. To test the significance of differences, Student's paired *t* test was used.

Results

The results are summarized in *Table I* and *Figs.* 1–3.

Effect of blood transfusion

Before blood transfusion the basal blood flow in the common femoral artery was 160 ± 58 ml/min. Following transfusion, it increased by, on average, 171 per

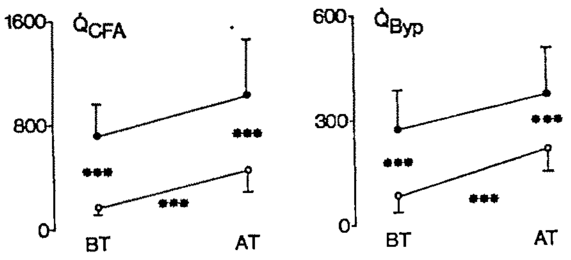

Fig. 1. Mean values of common femoral arterial and bypass blood flows ($\dot{Q}_{CFA}$, $\dot{Q}_{Byp}$ ml/min) before blood transfusion (BT) and after transfusion (AT) before (○——○) and after (●——●) pharmacological vasodilatation. $n = 11$. * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

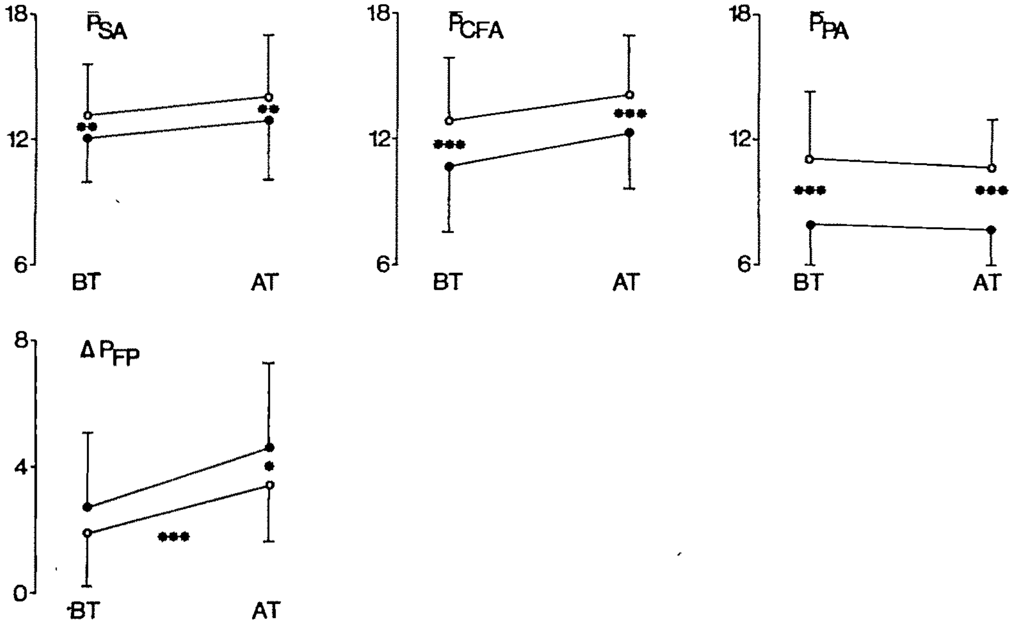

Fig. 2. Mean pressures in the subclavian, common femoral and popliteal arteries ($\bar{P}_{SA}$, $\bar{P}_{CFA}$, $\bar{P}_{PA}$ kPa) and mean femoropopliteal pressure difference (ΔP_{FP} kPa). Abbreviations as in *Fig.* 1. $n = 11$ except for $\bar{P}_{SA}$, where $n = 8$.

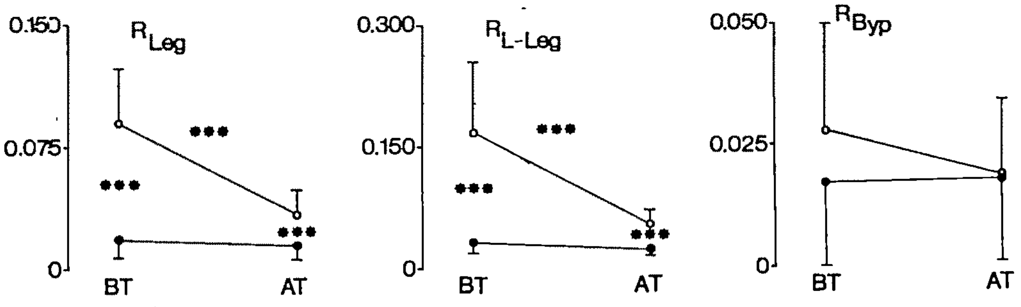

Fig. 3. Mean values for peripheral resistance for the whole leg, the lower leg and the bypass graft (R_{Leg}, R_{L-Leg}, R_{Byp} kPa min^{-1} ml^{-1}). Abbreviations as in *Fig.* 1. $n = 11$.

Table I: MEAN VALUES FOR INTRAOPERATIVE GRAFT FLOW RATE (ml/min), FEMOROPOPLITEAL PRESSURE DIFFERENCE (kPa) AND RUN-OFF RESISTANCE (kPa min^{-1} ml^{-1}) DURING FEMOROPOPLITEAL VEIN BYPASS RECONSTRUCTIONS GIVEN BY VARIOUS AUTHORS

		Flow rate		Femoropopliteal pressure difference		Run-off resistance	
	No. of cases	Basal	Maximal	Basal	Maximal	Basal	Maximal
Present study (before transfusion)	11	81	278	1·9	2·7	0·167	0·033
Present study (after transfusion)	11	215	373	3·4	4·6	0·054	0·023
Mannick et al. (1966)	14	49		0·9			
Barner et al. (1968)	28	60	240				
Mundt et al. (1969)	19	79		2·0		0·273	
Myhre et al. (1970)	29	100	228	1·0			
Bliss* (1973)	21	128	230			0·117	0·066
Dedichen (1973)	40	108	272	1·2			

* Four Dacron bypasses and endarterectomies.

cent, to 433 ± 159 ml/min ($P<0{\cdot}001$). The corresponding flow values in the bypass vein were 81 ± 46 and 215 ± 67 ml/min respectively, implying an increase of 165 per cent ($P<0{\cdot}001$) after transfusion. Simultaneous changes in blood pressures were much less pronounced and not significant ($P>0{\cdot}05$). Thus, after transfusion, the mean pressures in the subclavian and common femoral arteries increased from 13·2 ± 2·4 kPa and 12·9 ± 2·9 kPa respectively to 14·0 ± 3·1 kPa and 14·1 ± 2·8 kPa respectively. The mean pressure in the popliteal artery showed a slight, not significant decrease from 11·1 ± 3·2 kPa before blood transfusion to 10·7 ± 2·3 kPa after transfusion. However, as a result of these slight pressure changes in the common femoral and popliteal arteries, the femoropopliteal pressure difference increased significantly following blood transfusion from 1·9 ± 1·6 kPa to 3·4 ± 1·9 kPa ($P<0{\cdot}01$). Since the pressures in the common femoral and popliteal arteries were not significantly affected by transfusion, the increased femoral and bypass blood flow rates after transfusion must have been due to decreased vascular resistance in the leg. In fact, the mean vascular resistance for the whole leg and the lower leg decreased significantly ($P<0{\cdot}001$) after transfusion by 61 ± 14 per cent and by 62 ± 15 per cent respectively. The resistance over the graft was not affected by blood transfusion. After transfusion it was 0·019 ± 0·015 PRU.

Effect of pharmacological vasodilatation

Before blood transfusion vasodilatation caused an increase in common femoral arterial and bypass blood flows by, on average, 364 per cent to 719 ± 239 ml/min ($P<0{\cdot}001$) and by 274 per cent to 278 ± 109 ml/min ($P<0{\cdot}001$) respectively. Simultaneously, the mean femoral and popliteal blood pressures decreased significantly by 18 ± 7 per cent ($P<0{\cdot}001$) and 28 ± 10 per cent ($P<0{\cdot}001$) respectively. Consequently, parallel with the increase in common femoral arterial and bypass blood flow rates following vasodilatation was a decrease in vascular resistance in the whole leg and in the lower leg. This decrease in resistance following vasodilatation amounted to 81 ± 7 per cent ($P<0{\cdot}001$) in the whole leg, and 78 ± 8 per cent ($P<0{\cdot}001$) in the lower leg.

After blood transfusion there was still a significant increase in blood flow during vasodilatation. Thus, in the common femoral artery, the blood flow increased by, on average, 135 per cent to 1017 ± 429 ml/min ($P<0{\cdot}001$). The corresponding values for the bypass graft were 72 per cent and 373 ± 136 ml/min ($P<0{\cdot}001$) respectively. Also, after transfusion vasodilatation caused a significant decrease in the mean common femoral and popliteal arterial blood pressures by, on average, 14 per cent to 12·3 ± 2·7 kPa ($P<0{\cdot}001$) and 28 per cent to 7·7 ± 1·7 kPa ($P<0{\cdot}001$) respectively. Thus, a decreased vascular resistance in the whole leg and in the lower leg accompanied increased common femoral and bypass blood flows. However, these changes in vascular resistances following vasodilatation, though still significant, were less pronounced after blood transfusion as compared to values before transfusion. Thus, after transfusion, vasodilatation caused a decrease in whole leg resistance by 56 ± 9 per cent ($P<0{\cdot}001$) and in lower leg resistance by 57 ± 7 per cent ($P<0{\cdot}001$).

The pressure gradient over the bypass graft increased after vasodilatation. Before transfusion, however, the increase from 1·9 ± 1·6 kPa to 2·7 ± 2·4 kPa was not significant, while after transfusion the increase from 3·4 ± 1·9 kPa to 4·6 ± 2·8 kPa was statistically significant ($P<0{\cdot}05$). However, with these increases in pressure difference there were parallel increases in flow rates in the bypass graft. Resistance of the graft did not change significantly during vasodilatation neither before nor after transfusion. The graft resistance was low at each measurement: furthermore, following vasodilatation, it was less than the lower leg resistance, both before and after transfusion.

Blood pressure in the subclavian artery decreased significantly during vasodilatation by 8 ± 4 per cent ($P<0{\cdot}01$) before transfusion and by 8 ± 5 per cent ($P<0{\cdot}01$) after transfusion.

Graft patency

Based on history, the presence of a palpable pulse either in the graft or distal to it and oscillometric measurements, all patients had patent grafts and showed a marked improvement at follow-up 13–24 months (mean 18 months) after operation.

Discussion

In the present study it was shown that both an increase of the intravascular volume and the intra-arterial injection of a vasodilatory drug have a marked effect on vascular resistance in the leg.

Augmenting the intravascular volume by whole blood transfusion significantly decreased the peripheral resistance. As leg blood pressure was not significantly altered by transfusion, the decrease in vascular resistance was accompanied by a marked increase in blood flow.

The variation in leg resistance with different intravascular blood volumes explains the wide range of bypass flow values reported (*Table I*). Intravascular volume also affects the response to vasodilatation. Thus, the percentage flow increase in the graft after dilatation before blood transfusion was much higher than after transfusion. Therefore, the marked flow increase (+300 per cent) reported by Barner et al. (1968) may have been due to hypovolaemia and does not necessarily reflect the true physiological reactiveness of the distal vascular bed in a normovolaemic situation.

The presence of a residual femoropopliteal pressure difference after vein grafting was noted in all patients, although the reconstructions were successful. When the circulating blood volume was increased, the femoropopliteal pressure difference showed a further significant increase. The resistance of the graft itself, however, was unchanged following blood transfusion, implying that the increase in pressure difference was accompanied by an adequate flow increase in the bypass graft. The resistance of the bypass vein in all patients was less than that of the lower leg, indicating that the graft was functioning adequately and that it did not obstruct the blood flow.

From the present findings it is apparent that the femoropopliteal pressure difference does not *per se* indicate the capacity of the graft. The pressure difference should always be evaluated together with the blood flow through the graft. Thus, a significant increase in flow rate together with a moderate pressure gradient increase following blood transfusion indicates a good reconstruction, whereas an increase in pressure gradient without an accompanying flow increase indicates an ineffective bypass graft or a technical fault, such as too narrow an anastomosis. The resistance of the graft itself must also be related to the lower leg resistance. Thus, if the resistance of the graft is higher than that of the lower leg, the implication is that the graft obstructs the blood flow.

Compared with the results of other studies, the femoropopliteal pressure difference obtained in the present study after adequate blood substitution was high. Our opinion that the low femoropopliteal pressure difference previously reported was caused by hypovolaemia is supported by the fact that bypass flow values in the same patients were also low (*Table I*). This supports the importance of blood volume for the correct interpretation of a regional heamodynamic variable.

The further increase in femoropopliteal pressure gradient after vasodilatation reflects the relatively limited and fixed lumen capacity of the graft. We therefore do not support the contention of Bliss (1973) that an increase in pressure gradient after papaverine injection should indicate a technical fault. On the other hand, a major increase in pressure gradient might indicate a technical error or a graft with too small a calibre. However, in the present study, in 7 of the 11 patients the femoropopliteal pressure difference exceeded 3·0 kPa after adequate blood transfusion without the presence of a technical fault.

The peripheral resistance was also significantly altered by blood transfusion. The lower leg resistance (run-off resistance) before blood transfusion was within the same range as in the patients reported by Mundt et al. (1969) and by Bliss (1973), whereas resistance values in the present study after transfusion were significantly lower. This supports the idea that the patients reported by the quoted authors were hypovolaemic.

The injection of papaverine also markedly reduced the peripheral resistance. However, the decrease in resistance was significantly more pronounced before than after blood transfusion. Thus, the response to vasodilatation gives valuable information about the state of volume substitution. There was a significant decrease in subclavian, femoral and popliteal arterial pressures after vasodilatation, indicating a systemic effect exerted by papaverine after regional arterial injection. This should be taken into account when injecting this agent in a patient who is hypovolaemic to a significant degree.

The effect of papaverine on the peripheral resistance is important for a correct evaluation of the maximal flow capacity of the bypass graft. Thus, the flow rate obtained in the graft following papaverine injection after adequate volume substitution should be comparable to that following physiological stimulation, i.e. leg exercise, because, in the present investigation, the resistance in the leg following vasodilatation showed no marked difference before and after blood transfusion.

References

BARNER H. B., JUDD D. R., KAISER G. C. et al. (1968) Blood flow in femoropopliteal bypass vein grafts. *Arch. Surg.* **96**, 619–627.

BLISS B. P. (1973) Pressure, flow and peripheral resistance measurements during surgery for femoropopliteal occlusion (preliminary observations on 21 limbs). *Scand. J. Clin. Lab. Invest.* **31**, Suppl. 128, pp. 179–183.

CAPPELEN C. jun. and HALL K. V. (1964) The great saphenous vein used *in situ* as an arterial shunt after vein valve extirpation. *Acta Chir. Scand.* **128**, 517–525.

CAPPELEN C. jun. and HALL K. V. (1967) Electromagnetic blood flowmetry in clinical surgery. *Acta Chir. Scand.* Suppl. 368.

DEDICHEN H. (1973) Prognostic significance of intraoperative flow and pressure measurements in reconstructive vascular surgery. *Scand. J. Clin. Lab. Invest.* **31**, Suppl. 128, pp. 189–192.

ENGSTROM C. G. and HERZOG P. (1959) Ventilation nomogram for practical use with the Engstrom ventilator. *Acta Chir. Scand.* **37**, Suppl. 245.

HALL K. V. (1964) The arterial homograft used as 'bypass' in patients with femoropopliteal arteriosclerotic obstruction. *Acta Chir. Scand.* **127**, 353–366.

HOYE R. C., KETCHAM A. S. and BERLIN N. I. (1961) Total red cell volume changes associated with extensive surgery. *Surg. Gynecol. Obstet.* **112**, 697–701.

MANNICK J. A. and JACKSON B. T. (1966) Hemodynamics of arterial surgery in atherosclerotic limbs. 1. Direct measurement of blood flow before and after vein grafts. *Surgery* **59**, 713–720.

MUNDT E. D., DARLING R. C., MORAN J. M. et al. (1969) Quantitative correlation of distal arterial outflow and patency of femoropopliteal reversed saphenous vein grafts with intraoperative flow and pressure measurements. *Surgery* **65**, 197–206.

MYHRE H. O., DEDICHEN H., LAUEN O. et al. (1970) Peroperative trykk- og blodströmsmålinger ved rekonstruktive arteriekirurgi i underekstremitetene. *Tidsskr. Nor. Laegeforen.* **90**, 1871–1873.

SCHENK W. G. and DEDICHEN H. (1967) Electronic measurement of blood flow. *Am. J. Surg.* **114**, 111–118.

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Solitary toxic adenoma of the thyroid gland

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SUMMARY

The incidence of solitary toxic adenoma of the thyroid in a general surgical unit with an interest in thyroid disease has been reviewed over a 15-year period. Six hundred and thirty thyrotoxic cases were treated surgically, 35 (5·6 per cent) having a solitary toxic adenoma. Thyroid enlargement or toxicity had been present for more than 5 years in 7 patients (20·0 per cent). Cardiovascular complications were present in 6 cases (17·1 per cent).

Thyroid lobectomy resulted in 30 (85·7 per cent) euthyroid and 5 (14·3 per cent) hypothyroid patients. One toxic adenoma contained a focus of carcinoma. The clinical features, diagnosis and management of solitary toxic adenoma, and the management of symptomatic nodules which are 'hot' but not biochemically toxic, are discussed.

THE pathological diagnoses of patients undergoing surgery for thyroid disorders in one unit of the Sheffield Royal Infirmary over the 15 years 1963–77 were reviewed retrospectively. The radioisotope thyroid scans performed in the hospital between these years were also surveyed. The clinical details, biochemical and scan data, operative findings and histological material of patients with a possible solitary toxic adenoma were then examined.

Patients and methods

Between 1963 and 1977 a total of 1228 patients in the unit underwent thyroid operations. Six hundred and thirty patients were thyrotoxic (51·3 per cent). A total of 165 solitary adenomas was removed, of which 35 were toxic, representing 21·2 per cent of the adenomas and 5·6 per cent of the total toxic cases managed surgically (*Table I*). Seven cases of solitary adenoma had clinical features suggesting thyrotoxicosis, but protein-bound-iodine and radio-iodine uptake levels were normal. These patients have been classified as having solitary non-toxic adenomas.

Table I: OPERATIONS FOR TOXIC THYROID DISEASE 1963–77

Diagnosis	No.	%
Graves's disease (toxic hyperplasia)	367	58·2
Toxic multinodular goitre	228	36·2
Solitary toxic adenoma	35	5.6
Total	630	100

The mean age of patients with solitary toxic adenoma was 49·7 (±13·4 s.d. years) with a range of 24–76 years. The mean age of patients with solitary non-toxic adenoma was younger, at 41·8 (±13·7 s.d. years) and a range of 13–78 years.

The maximum incidence of solitary toxic adenoma was in the decade 50–59 years (11 of 35 cases), whereas that of solitary non-toxic adenomas was in the 30–39-year period (30 of 135 cases) (*Fig.* 1). A 2 × 2 contingency test dividing the two groups at age 45 years shows this to be a significant difference ($P < 0·001$). In contrast, the mean age of patients undergoing surgery for Graves's disease (toxic hyperplasia) was 31·5±9·4 years (range 15–67) and that for toxic multinodular goitre 43·9± 13·7 years (range 15–78).

The sex incidence of toxic adenoma did not differ significantly from that of the other types of thyrotoxicosis or thyroid carcinoma. Of the cases of solitary toxic adenoma, 94·3 per cent were female, compared with 81·5 per cent for solitary non-toxic adenoma. Among patients with other conditions undergoing thyroid surgery the female incidence was 88·4 per cent for Graves's disease, 87·8 per cent for toxic multinodular goitre and 80·4 per cent for carcinoma.

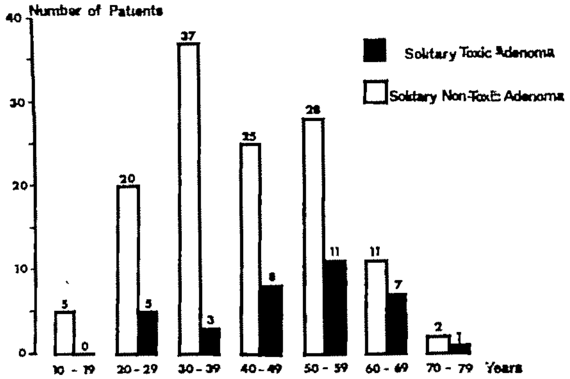

Fig. 1. Age incidence of solitary toxic adenomas and solitary non-toxic adenomas by decades.

Clinical features

The presenting complaint in 19 (54·3 per cent) of the 35 solitary toxic adenoma cases was the thyroid nodule itself. In 13 of these it had been present for 1 year or more, 2 patients claiming to have had a goitre since adolescence. A 53-year-old woman gave a 13-year history of a slowly enlarging lump in the neck, which had on two occasions been associated with toxicity and treated by radio-iodine. Despite this, the nodule had continued to enlarge and she came to surgery for pressure symptoms. In contrast, one patient presented with a 5-week history of a thyroid nodule first noticed after an upper respiratory tract infection, and slight symptoms of toxicity.

Only 13 cases (37·1 per cent) presented with symptoms of thyrotoxicosis. Irritability and anxiety predominated in 5, the symptoms being present for between 1 and 13 years. Three patients presented with weight loss, 3 with cardiovascular complications (one being diagnosed by her practitioner after a one-day episode of faintness and sweating) and one with menstrual irregularity. In 3 patients the toxic adenoma was found incidentally during the investigation of pulmonary, dermatological and arthritic problems. However, nearly all the patients had thyrotoxic symptoms on inquiry, sometimes only mild or intermittent, and these had often been present for many years.

Clinical examination revealed a solitary nodule in 18 (51·4 per cent) patients. In a further 9 cases a unilobar thyroid enlargement was noted, and in these cases at surgery the adenoma was found to occupy the major portion of one lobe. Four patients were thought to have a diffusely enlarged thyroid, 2 a multinodular goitre, 1 a retrosternal goitre and 1 a normal thyroid gland. The thyroid status was frankly toxic in 15 patients (42·9 per cent) and mildly toxic in 13 (37·1 per cent), whilst 7 (20·0 per cent) were thought to be euthyroid. Cardiovascular complications were present in 6 patients (17·1 per cent), 4 being in atrial fibrillation and 2 in congestive failure, their mean age being 63·5±4·8 years (range 56–69) compared with a mean age of 49·7 years for the group as a whole.

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Table II: BIOCHEMICAL AND HISTOLOGICAL DATA

Sex	Age (yr)	PBI (0·3–0·63 μmol/l)	^{131}I uptake test 4-h (15–40%/l)	48-h (20–50%/l)	48-h PB^{131}I (<0·30%/l)	Histology
F	48	0·53	(T$_3$ 6·9 nmol/l: T$_4$ 112 nmol/l)			Simple
F	49	0·60	44	44	2·37	Simple
F	45	0·61	(T$_3$ uptake test toxic range)			Macrofollicular
F	47	0·62	49·6	61	0·73	Macrofollicular
F	61	0·62	39	45	0·83	Simple
F	24	0·65	23	27	1·18	Simple
F	56	0·65	38	49	—	Simple
F	50	0·66	36	49	0·38	Simple
F	28	0·66	36	19	3·80	Simple
F	46	0·67	—	—	—	Simple
F	47	0 69	—	—	—	Simple
F	66	0·70	—	—	—	Macrofollicular
F	76	0·70	29	69	0·23	Macrofollicular
F	35	0·70	67	58	1·64	Simple
F	47	0·73	48	60	0·31	Simple
F	27	0·73	—	—	—	Macrofollicular
F	48	0·76	49	38	2·50	Simple
F	25	0·76	39	49	0·39	Macrofollicular
F	27	0·76	—	—	—	Simple
F	56	0·78	—	—	—	Microfollicular
F	35	0·79	41	64	0·30	Macrofollicular
F	63	0·79	61	58	1·87	Microfollicular
F	66	0·82	—	—	0·62	Macrofollicular
F	57	0·83	44	54	0·89	Macrofollicular
F	50	0·86	53	—	0·92	Macrofollicular
F	69	0·88	—	—	—	Simple
F	57	0·89	41	52	0·26	Macrofollicular
F	59	0·90	—	—	—	Microfollicular
F	37	0·96	40	48	1·93	Simple
F	53	0·96	—	—	—	Simple
F	52	0·97	50	52	1·65	Macrofollicular
F	56	0·98	32	45	0·66	Simple
F	53	1·19	48	38	2·18	Microfollicular
M	62		(T$_3$ 4·69: T$_4$ 182 nmol/l)			Macrofollicular
F	53	—	32	54	0·54	Microfollicular

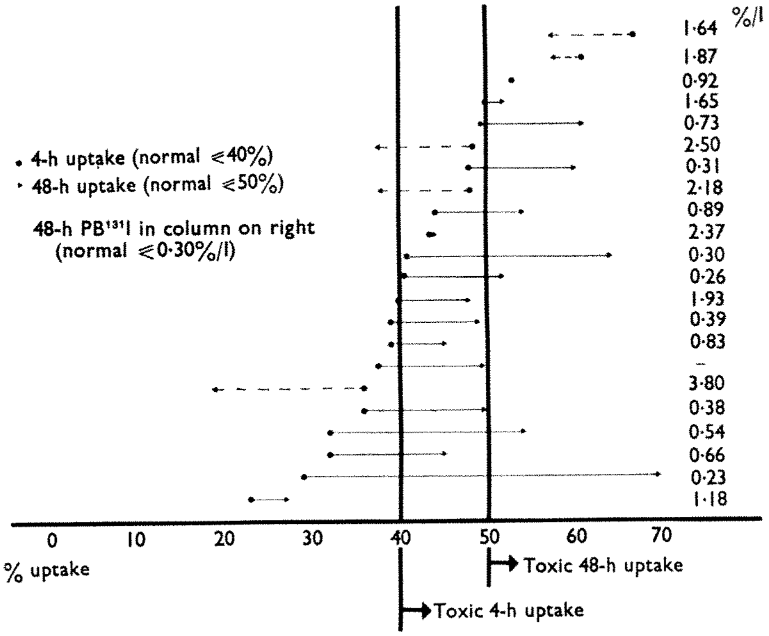

Fig. 2. Results of radio-iodine uptake tests in solitary toxic adenomas.

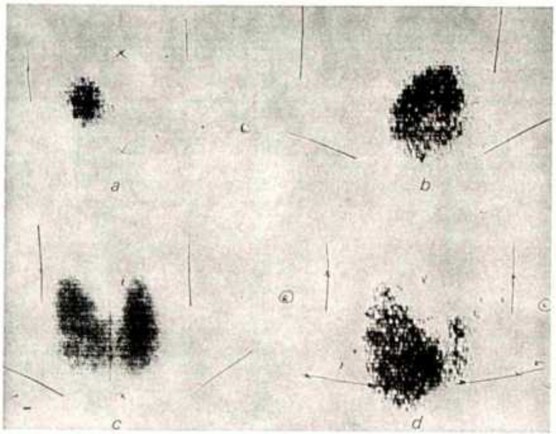

Fig. 3. Thyroid scans. *a*, Small 'T_3-toxic' adenoma in the right lobe. *b*, Large T_4 adenoma replacing left lobe. *c*, Graves's disease. *d*, Toxic multinodular goitre.

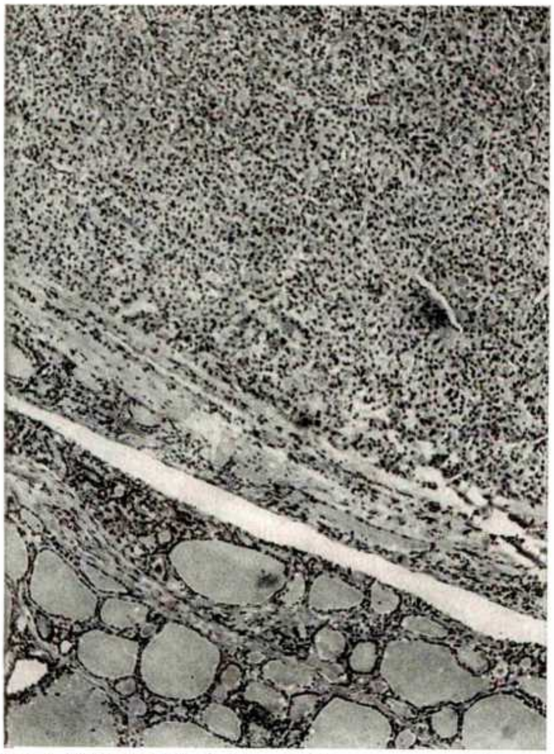

Fig. 4. 'Microfollicular' adenoma. Homogeneous cellular structure of the adenoma, separated by capsule from compressed normal thyroid follicles in the lower part of the field. (HE. ×53.)

In the 7 patients with solitary adenomas who were clinically but not biochemically toxic, 5 complained of the thyroid nodule or its recent enlargement.

None of the toxic adenoma patients had exophthalmos, or any other eye signs.

Biochemical investigations

Over the 15-year period, protein-bound-iodine (PBI) was the basis of the biochemical diagnosis of toxicity, often in conjunction with an *in vivo* thyroidal ^{131}I uptake test and a T_3

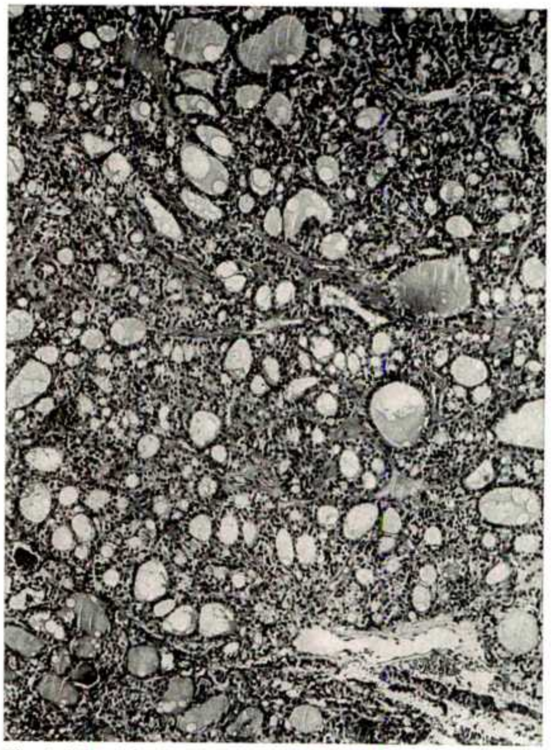

Fig. 5. 'Simple' adenoma. Structure resembles a normal thyroid gland. (HE ×53.)

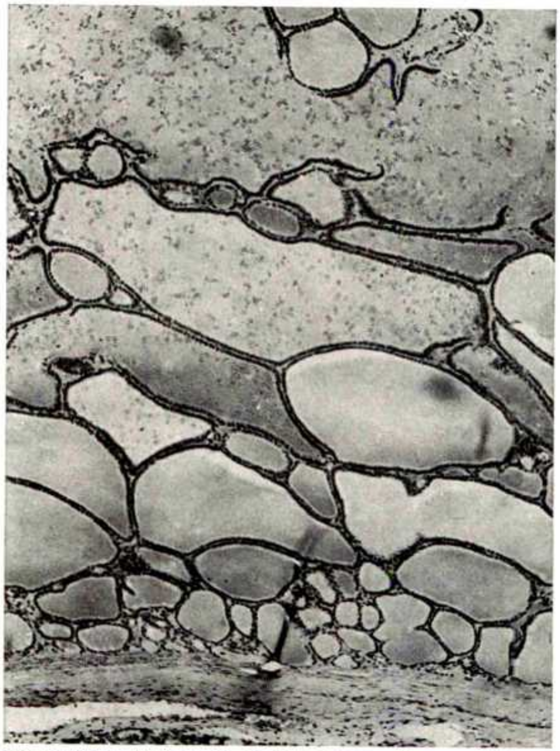

Fig. 6. 'Macrofollicular' (colloid) adenoma. Large colloid-filled acini separated by capsule from compressed normal thyroid below. (HE ×53.)

(tri-iodo-thyronine) resin uptake test, as described by Barnett et al. (1973) (*Table II*).

The mean PBI at the time of diagnosis of toxic adenoma was 0·77±0·14 s.d. μmol/l (range 0·53–1·19 μmol/l), the normal range being 0·30–0·63 μmol/l. Four patients had a PBI in the high normal range, at 0·60, 0·61, 0·62 and 0·62 μmol/l, associated with toxic values for the ^{131}I uptake test or T$_3$ resin uptake test.

The ^{131}I uptake test was performed in 22 patients and gave toxic levels at 4 h (over 40 per cent uptake) in 13 patients (59·1 per cent) and at 48 h (over 50 per cent uptake) in 10 cases (45·5 per cent) (*Fig.* 2). The 48-h PB^{131}I was at a toxic level (over 0·30 per cent/l) in 19 cases (86·4 per cent), mean 1·19± 0·94 per cent/l, range 3·80–0·31 per cent/l).

Two patients had elevated T$_3$ levels at 4·69 nmol/l and 6·90 nmol/l (normal 1·23–3·07 nmol/l). In the first of these the thyroxine (T$_4$) was also raised at 182 nmol/l (normal 60–170 nmol/l). In the second T$_4$ was normal at 112 nmol/l, and this case is the only proved 'T$_3$-toxic' solitary adenoma in the series, but the T$_3$ and T$_4$ assays only became available in the last year of the survey.

Radioisotope scanning

Radio-iodine scanning commenced in the second year of this survey and was superseded by pertechnetate scintiscans for the latter 7 years. A total of 6967 thyroid scans was reviewed and 155 images suggestive of solitary 'hot' lesions identified in patients from the Sheffield Royal Infirmary. Thirty patients proved to have a solitary toxic adenoma (*Fig.* 3). The additional 5 in the series did not have scans, but their thyrotoxicosis was cured by lobectomy and was presumed to be due to the contained adenoma. A further 21 solitary autonomous toxic nodules arose within a multinodular goitre.

Pathology

The strict histopathological criteria of Meissner and Warren (1969) were applied before a solitary lesion was accepted as an adenoma. A well-encapsulated solitary nodule with a structure differing from that of the adjacent compressed normal gland was considered a true adenoma. The presence of two or more nodules usually indicated an area of multinodular goitre rather than an adenoma. Seventeen solitary toxic nodules due to multinodular goitre were excluded from the series. Solitary adenomas within toxic multinodular goitres were also excluded. Adenomas were subdivided into the cellular, relatively poorly differentiated, 'microfollicular' variety (*Fig.* 4), with minimal colloid or acinar structure, 'simple', well-differentiated adenomas whose structure approximated to that of the normal gland (*Fig.* 5), and 'macrofollicular' (colloid) adenomas with greatly distended acini containing excessive colloid (*Fig.* 6). Hürthle cell adenoma, derived from variants of follicular cells with excessive and abnormal mitochondria, was the final category recognized. There was considerable variation of histological pattern within each adenoma, limiting the value of such subdivisions.

Twenty-two of the 35 solitary toxic adenomas (62·9 per cent) were of the relatively cellular microfollicular and simple varieties. In contrast, 83 of the 130 non-toxic solitary adenomas (63·8 per cent) were of the macrofollicular variety (*Table III*).

Degeneration, either visible grossly or microscopically, involving one-third or more of the adenoma was seen in 11 solitary toxic adenomas (31·4 per cent) and in 83 solitary non-toxic adenomas (63·8 per cent) (*Table III*, *Fig.* 7).

A focus of papillary carcinoma was identified in one toxic macrofollicular adenoma. Possible malignant change was also seen in one macrofollicular adenoma from a patient clinically, but not biochemically, toxic.

Surgical management

Unilateral thyroid lobectomy has been the policy throughout the 15 years. Thyrotoxicosis was controlled with carbimazole, usually commencing with 15 mg strictly 8-hourly and then reducing as the patient became euthyroid. Preoperative therapy with potassium iodide was not regarded as necessary in this condition, and in this unit it is no longer used preoperatively in any type of thyrotoxicosis. If at operation the solitary nodule was confirmed, the opposite lobe was inspected but otherwise not disturbed, thereby eliminating the risk of postoperative hypoparathyroidism. Identification of the recurrent laryngeal nerve was routinely performed and parathyroid gland identification attempted. Wound management was facilitated by a suction drain and Michel clips, both being removed 2 days postoperatively. The usual hospitalization period was 4–5 days.

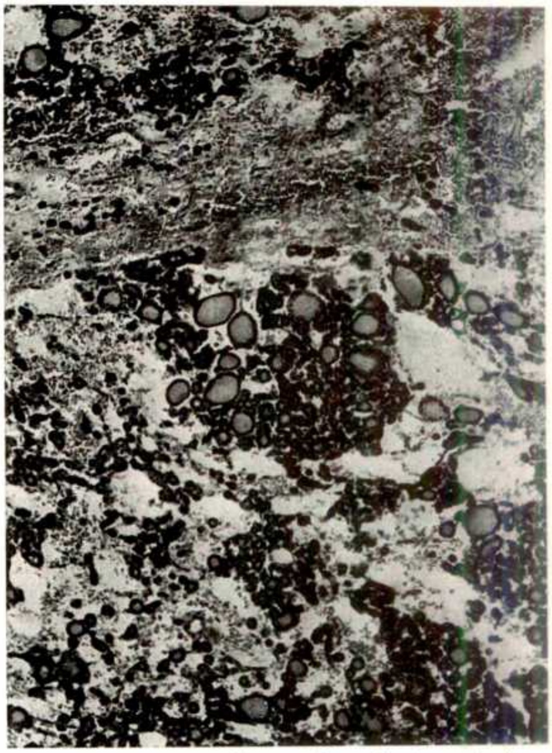

Fig. 7. Degeneration and haemorrhage affecting a simple adenoma. (HE ×53.)

Table III: HISTOLOGICAL DATA

Histological variety	Solitary toxic adenoma	Solitary non-toxic adenoma
Microfollicular	5 (14·3)	15 (11·6)
Simple	17 (48·6)	30 (23·2)
Macrofollicular	13 (37·1)	83 (63·8)
Hürthle cell	0	2 (1·4)
Haemorrhage and degeneration	11 (31·4)	83 (63·8)

Figures in brackets are percentages.

Results

Following unilateral thyroid lobectomy in the 35 patients with solitary toxic adenoma, there was no operative mortality and no significant early postoperative morbidity. After a mean follow up of 6·3± 3·9 (s.d.) years (range 0·5–15), 30 patients (85·7 per cent) remain euthyroid clinically and biochemically. Five patients (14·3 per cent) have become hypothyroid. This was detected in 2 cases 1 month postoperatively, in a further 2 cases at 3 and 8 months respectively and in 1 case at 18 months. Five other patients have developed varied conditions. Two cases of depression occurred at 4 and 11 months postoperatively, a single fatal case of breast carcinoma in a euthyroid patient 5 years postoperatively and single cases of disseminated sclerosis and senile dementia several years postoperatively.

The further 7 patients with solitary adenoma, clinically but not biochemically toxic, have all remained euthyroid following lobectomy.

Discussion

Clinical features and difficulties in diagnosis

Henry Plummer (1913) first differentiated toxic adenoma from exophthalmic goitre, and it has remained a rare but interesting cause of thyrotoxicosis (Cope et al., 1947; Roualle, 1949; Montgomery and Welbourn, 1975). This survey establishes an incidence of 5·6 per cent for solitary toxic adenoma amongst thyrotoxic cases managed surgically in an area with a high goitre incidence.

The often mild toxicity and absence of eye signs may make the diagnosis elusive. Prolonged mental and physical ill health may result. Nineteen patients (54·2 per cent) complained of irritability and anxiety, often of some years' duration, whilst 6 patients (17·1 per cent) developed cardiovascular complications, emphasizing the dangers of the missed diagnosis. Ramsay et al. (1972) suggested that the adenomas may secrete to toxic levels only intermittently. The occurrence of degeneration accompanied by regeneration in adjacent areas in one-third of the toxic adenomas might explain this.

In the hyperthyroid patient the solitary 'hot' area on a scan is the key to diagnosis (*Fig.* 3), radioisotope uptake in the remainder of the thyroid being suppressed. Repeated evaluation of T_4 and T_3 levels may be required in suspect cases to confirm toxicity biochemically. It is of interest that in the single example of a 'T_3-toxic' adenoma in this series, the PBI was normal at 0·53 μmol/l. Possibly some of the patients with toxic symptoms but a normal PBI had 'T_3-toxic' adenomas before the T_3 assay became available. The value of the ^{131}I uptake test, especially the 48-hour $PB^{131}I$, which was elevated in nearly all those tested, is diminished by the findings of Fellinger et al. (1961) that the 48 hour $PB^{131}I$ is raised in most cases of hyperactive nodules regardless of whether the patient is toxic. The autonomous nature of the adenoma may be demonstrated by a scan after administration of thyroid-stimulating hormone and by its continued uptake of iodine in the T_3 suppression test. This test, however, has dangers in the elderly in whom cardiac dysrhythmia may be precipitated, and it is no longer necessary now that the thyroid-releasing hormone test is available.

Advantages of surgical management

The solitary toxic adenoma, with its high iodine avidity in an otherwise suppressed gland, seems the perfect candidate for radio-iodine therapy. Yet 4 of the 35 toxic adenomas managed surgically had failed to respond to radio-iodine. The ^{131}I uptake data (*Table II*, *Fig.* 2) indicate a fast uptake into a small iodine pool with rapid turnover (Fellinger et al., 1961; Ramsay et al., 1972). In 5 cases the 48-h uptake was already lower than the 4-h uptake, and the 48-h $PB^{131}I$ was markedly elevated. Structurally, these 5 adenomas were the more cellular microfollicular and simple varieties with little colloid storage. This rapid uptake, metabolism and release of radio-iodine implies that it might not remain within the adenoma long enough to be therapeutically effective.

In contrast, surgery rapidly controlled the thyrotoxicosis and was relatively complication-free. It was anticipated that the suppressed lobe would recover and the patient remain euthyroid. This failed to occur in 5 cases (14·3 per cent). The non-adenomatous tissue in the rest of the excised lobe appeared normal with no evidence of significant thyroiditis. Two patients had had prolonged antithyroid therapy before surgery—two courses of radio-iodine in one patient and carbimazole for 10 years in another. Presumably, the remaining lobe was functionally impaired, and both patients became hypothyroid immediately postoperatively, although Michie et al. (1972) and Pegg et al. (1973) demonstrated no correlation between antithyroid drug therapy and postoperative hypothyroidism.

In a further case the residual lobe was noted to be very atrophic and hypothyroidism developed 3 months postoperatively. Prolonged antithyroid therapy or a very small contralateral lobe might therefore be indications for a lesser excision than complete lobectomy. Two patients with normal residual lobes became hypothyroid at 8 and 18 months postoperatively. Careful postoperative follow-up is essential. Blum et al. (1975) managed 6 cases by excision with no postoperative hypothyroidism. In contrast, Molnar et al. (1965) reported 3 cases of postoperative hypothyroidism out of 11 toxic nodules managed surgically, 2 of the hypothyroid patients having undergone subtotal thyroidectomy. Three of the patients in our series were treated as hypothyroid on biochemical evidence early in the postoperative period. We would prefer to withhold thyroxine and accept minor clinical features of hypothyroidism with reduced thyroid hormone levels for some months. In our experience, such patients recover presumably due to reactivation of the residual lobe by endogenous thyroid-stimulating hormone.

A further advantage of surgery is indicated by the patient whose toxic adenoma contained a focus of papillary carcinoma, and the other patient with a possibly malignant area in a 'hot', clinically toxic adenoma. 'Hot' nodules on scan are held to be rarely malignant (Wade, 1975; Editorial, 1977). Johnston (1975) warns of a 4 per cent malignancy rate in 'functioning nodules' and Hamburger (1975) found 3 cases of coexistent carcinoma in 29 patients with 'autonomously functioning thyroid lesions', one being a focus of papillary carcinoma in a solitary toxic lesion. Lobectomy with follow-up is adequate management for the unsuspected papillary carcinomas in this situation (Johnston, 1975).

Management of autonomous adenoma not provenly toxic

Proponents of a conservative policy argue that the probability of a 'hot' nodule becoming toxic is low (Langarten and Spencer, 1973). In some cases degeneration and self-cure may ensue (Miller and Block, 1968), such changes being detected on serial ultrasound or radioisotope scans. However, the prolonged duration of symptoms in many cases of toxic adenoma in this series does not support this idea.

Certainly, degeneration was seen in one-third of the solitary toxic adenomas and in nearly two-thirds of the solitary non-toxic adenomas. However, this is one phase in a cycle and is likely to be followed by regeneration. The age distribution of toxic and non-toxic adenomas suggests a trend towards development of toxicity with time rather than the reverse.

In this series, 7 symptomatic patients with solitary autonomous adenomas who were clinically but not biochemically toxic were managed by lobectomy. All have remained euthyroid. It is notable that in 5 patients it was the thyroid nodule or its recent enlargement which was the main complaint. Lobectomy provides a rapid resolution of the patient's problem and the doctor's dilemma.

Acknowledgements

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References

BARNETT D. B., GREENFIELD A. A., HOWLETT P. J. et al. (1973) Discriminant value of thyroid function tests. *Br. Med. J.* **2**, 144–146.

BLUM M., SHENKMAN L. and HOLLANDER C. S. (1975) The autonomous nodule of the thyroid: correlation of patient's age, nodule size and functional status. *Am. J. Med. Sci.* **269**, 43–50.

COPE O., RAWSON R. W. and MCARTHUR J. W. (1947) The hyperfunctioning single adenoma of the thyroid. *Surg. Gynecol. Obstet.* **84**, 415–425.

EDITORIAL (1977) Diagnosing thyroid nodules. *Lancet* **2**, 1268.

FELLINGER K., HÖFFERM R., EGERT H. et al. (1961) Clinical and laboratory observations in patients with hyperactive thyroid nodules. In: PITT-RIVERS R. (ed.) *Advances in Thyroid Research*. Oxford, Pergamon Press, p. 67.

HAMBURGER J. I. (1975) Solitary autonomously functioning thyroid lesions. *Am. J. Med.* **58**, 740–747.

JOHNSTON I. D. A. (1975) The surgery of thyroid cancer. *Br. J. Surg.* **62**, 765–768.

LANGARTEN S. and SPENCER R. P. (1973) A study of the natural history of 'hot' thyroid nodules. *Yale J. Biol. Med.* **46**, 259–263.

MEISSNER W. A. and WARREN S. (1969) *United States Armed Forces Atlas of Tumour Pathology*, 2nd series, Fascicle 4.

MICHIE W., PEGG C. A. S. and BEWSHER P. D. (1972) Prediction of hypothyroidism after partial thyroidectomy for thyrotoxicosis. *Br. Med. J.* **1**, 13–17.

MILLER J. M. and BLOCK M. A. (1968) The autonomous functioning thyroid nodule. *Arch. Surg.* **96**, 386–390.

MOLNAR G. D., WILBER R. D., LEE R. E. et al. (1965) On the hyperfunctioning thyroid nodule. *Mayo Clin. Proc.* **40**, 665–684.

MONTGOMERY D. A. D. and WELBOURN R. B. (1975) *Medical and Surgical Endocrinology*. London, Arnold, p. 281.

PEGG C. A. S., STEWARD D. J., BEWSHER P. D. et al. (1973) The surgical management of thyrotoxicosis. *Br. J. Surg.* **60**, 765–769.

PLUMMER H. S. (1913) The clinical and pathological relationship of simple and exophthalmic goitre. *JAMA* **61**, 650–651.

RAMSAY I., MARSDEN P., RICHARDSON P. J. et al. (1972) Thyroid 'hot' nodules. *Postgrad Med. J.* **48**, 577–583.

ROUALLE H. L. M. (1949) The solitary thyroid nodule and thyrotoxicosis. *Br. J. Surg.* **36**, 312–314.

WADE J. S. H. (1975) The aetiology and diagnosis of malignant tumours of the thyroid gland. *Br. J. Surg.* **62**, 760–763.

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A case of craniocleidal dysostosis presenting with vascular complications

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SUMMARY

A case of craniocleidal dysostosis was presented. In spite of the skeletal abnormalities present, the disease was not diagnosed until the patient, a married woman of 63, developed ischaemia of her right upper limb, followed by cerebral symptoms. An arch aortogram demonstrated an occlusion of the first part of the right subclavian artery involving the origin of the vertebral artery and a post-stenotic dilatation of the left subclavian artery due to costoclavicular compression. Such vascular abnormalities have not been previously described in this condition.

CRANIOCLEIDAL dysostosis is a relatively rare congenital condition in which there are skeletal and other anatomical abnormalities due to errors in the primary ossification of certain bones.

According to Abram (1907), the first description of the disease as a pathological entity was by Marie and Sainton (1898) who studied two affected families. In one family the disease was transmitted from the father to the son; in the other family the transmission was from mother to daughter. They named the disease 'la dysostose cleido-cranienne héréditaire' and defined the syndrome as a hereditable condition characterized by aplasia of the clavicles and overdevelopment of the transverse diameter of the cranium, coincident with delay in the ossification of the fontanelles.

The consistent involvement of the clavicles is attributable to the fact that the responsible genetic defect involves primarily those bones ossified earliest in fetal life, and the clavicle takes precedence as it is the first bone to be formed in the body. Primary centres appear in the mid-portion of the clavicle during the 6th week of intrauterine life. (The next bone in the body to ossify is the vault of the skull in which primary centres of ossification appear between the 6th and 8th weeks of intrauterine life.) Other bones less frequently involved include the lateral arches of the spine, pelvis, hip joints and the bones of the hands and feet.

Structural abnormalities in the clavicle range from a localized osseous defect in one clavicle to total absence of both clavicles. Usually when both clavicles are severely affected other gross anatomical defects are also present. The apex of the thorax is narrowed with the upper ribs drooping downwards and forwards with apparent lengthening of the neck (*Fig.* 1). The muscles normally attached to the clavicles may be vestigial, absent or have anomalous ligamentous attachments. The scapulas are frequently abnormal, being small, triangular in shape and more mobile than usual. In some cases the scapulas fail to articulate with the lateral remnants of the clavicle. It may be that most of these structural abnormalities are secondary due to faulty moulding consequent upon the collapse of the shoulder-girdle at a very early stage in the development of the fetus.

Soule (1946) found from a review of the literature that in a total of 323 cases, 198 were familial while 125 cases were sporadic. Both sexes were affected to an approximately equal extent, and the condition was transmitted through either parent with about equal frequency. According to Lasker (1946) the disorder is an autosomal dominant inheritance with the isolated cases being due to the frequent occurrence of a dominant mutation.

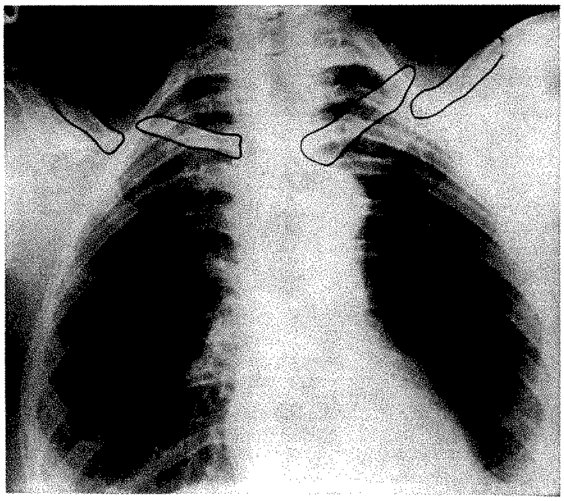

Fig. 1. Chest X-ray showing deformity of the upper thorax and the position of the clavicular fragments.

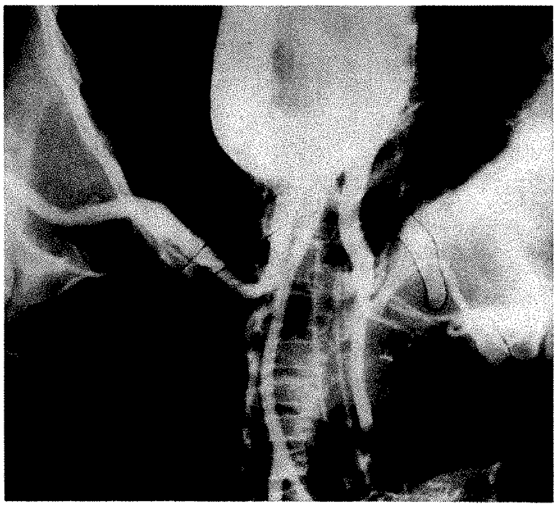

Fig. 2. Arch aortogram showing proximal occlusion of the right subclavian artery, involving the origin of the right vertebral artery. There is post-stenotic dilatation of the left subclavian artery.

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Case report

Mrs H. M. knew since her childhood that she was 'double-jointed', in that she could approximate her shoulders and she was unaware of any other member of her family having had the same facility. Until 1966 she enjoyed reasonably good health. In 1966, at the age of 53, she developed recurrent attacks of chest pain which her doctor described as being 'atypical of angina'. She had also recently acquired a bruising tendency which was apparently spontaneous. She was referred to the medical outpatient clinic. On examination she was normotensive. An ECG tracing was reported as showing 'a degree of posterior myocardial ischaemia'. A full haematological assessment showed no abnormality to account for the bruising. She did not have a chest X-ray. No further appointment was made.

In 1975, at the age of 63, she was referred to the surgical outpatient clinic with a history of having developed, during a 'flu-like illness 2 weeks before, sudden and severe ischaemia of her right arm. When seen at the clinic, the right upper limb was ischaemic. The subclavian pulse on the right side was normal, but pulses distal to this were absent. The pulses on the left side were normal. Both femoral pulses were present. An ECG was reported as 'showing recent myocardial ischaemia'. An X-ray of the chest was reported as 'showing narrowing of the thorax. Both clavicles are hypoplastic with pseudoarthrosis. The scapulas are abnormally placed and are triangular in shape. The findings are consistent with cranio-cleido-dysostosis'.

A diagnosis of axillary embolism, probably cardiac in origin, was made. As the condition had stabilized and there had already been a degree of spontaneous improvement in the circulation to the right hand, surgical intervention was not considered and the patient was allowed home.

In June 1977 she was admitted to a medical ward with a cerebrovascular incident, having the features of acute vertebral–basilar ischaemia. The symptoms recovered spontaneously after a period of bed rest. ECG and cardiac enzymes were normal. It was noted that the right subclavian pulse which had been present at the previous examination was now absent. An arch aortogram (*Fig.* 2) was performed and showed the following:

Right subclavian artery: There was thrombotic occlusion of the first part of the subclavian artery which apparently also involved the origin of the left vertebral artery, which was not visualized at any phase of the aortogram. Only in the late films was there any trace of the contrast medium in the axillary and brachial arteries.

Left subclavian artery: The left subclavian artery was compressed between the first rib and the proximal portion of the left clavicle with a large post-stenotic aneurysm which was both elongated and kinked. There was no filling defect in the aneurysm suggestive of a mural thrombus.

After complete recovery from her cerebral symptoms the patient was allowed home to return at a later date. She had no recurrence of her cerebral symptoms and her only complaint was of continued discomfort and loss of power in her right hand.

At operation the neck was explored through bilateral supraclavicular incisions. On the *right side* the anatomy of the posterior triangle of the neck was grossly distorted by the deformity of the upper ribs and the deflections of the clavicular fragments. The scalene and other muscles in the posterior triangle were vestigial and difficult to identify, as was also the phrenic nerve. Occlusion of the first part of the subclavian artery was confirmed as was the absence of pulsation in the right vertebral artery. An upper dorsal sympathectomy was impracticable for anatomical reasons, and the wound was closed.

On the *left side* the anatomy was similar except that the subclavian artery was compressed between the first rib and the proximal fragment of the clavicle with post-stenotic dilatation of the left subclavian artery. Removal of the proximal fragment of the clavicle relieved the proximal arterial stenosis. The subclavian aneurysm was not resected.

Discussion

Craniocleidal dysostosis is uncommon, and despite the seemingly obvious presence of cranial and clavicular abnormalities, the condition is often not recognized until adult life. Affected persons have a normal expectation of life, and most are healthy, intelligent and capable of hard physical labour (Lasker, 1946).

Soule (1946) concluded from his review that the clavicular defects were of little or no significance as far as function was concerned, for those involved rarely complained of difficulty in using their arms or shoulders, whether taking part in manual work or in sporting activities. He cites the example of one of his patients, a baggage master, who was able to handle heavy trunks and crates without difficulty. Maddox (1946) quotes a similar experience with a stoker in the Royal Australian Navy during World War II. Davis (1954) had a patient who, retrospectively, credited to this anomaly his exceptional ability as a college wrestler to 'wriggle out of any hold'.

Lasker (1946), in a carefully documented survey of over 500 cases collected from the world literature, found only 2 examples of cases in which significant neurological or vascular symptoms had been present.

1. Jones (1937) reported the case of a girl born of normal parents whose only skeletal defect was bilateral pseudoarthrosis of her clavicles. At the age of 17 she complained of pain along the inner aspects of both arms when carrying heavy objects. At a subsequent operation, the clavicles were stabilized by insertion of bone grafts between the two fragments of each clavicle. The graft on the left side was successful with relief of symptoms; the graft on the right side failed owing to sepsis, and the graft had to be removed. She continued to have symptoms when this shoulder was depressed. She subsequently married, and had a son with the classic features of craniocleidal dysostosis.
2. Poynton and Davies (1914) had a patient with craniocleidal dysostosis. She was a girl of 20, who was unable to work as a dressmaker because of shooting pains down the inner side of her right arm and over the front of her chest. On examination, there was marked loss of power in her right hand, and when the shoulder was depressed the radial pulse was diminished. At operation, the outer fragment of the right clavicle appeared to be pressing on the brachial plexus, and it was therefore removed. This gave dramatic relief of her acute symptoms although she continued to have some discomfort in her shoulders when sitting over her work. This was relieved by sitting up and bracing her shoulders.

It is relevant to note that both these patients were young women at an age when costoclavicular symptoms related to posture are not uncommon amongst otherwise healthy females.

In spite of the very large number of cases of craniocleidal dysostosis scrutinized by Lasker and others, there is no reference to pathological lesions of the subclavian arteries, whether aneurysmal or occlusive, which might be attributable to the costoclavicular anomalies present. The case presented here is unique in this respect.

References

ABRAM J. H. (1907) Cleidocranial dysostosis. *Lancet* **2**, 429–432.

DAVIS P. L. (1954) Deafness and cranio-cleido-dysostosis. *Arch. Otolaryngol.* **59**, 602–603.

FITCHET S. M. (1929) Cleido-cranial dysostosis: hereditary and familial. *J. Bone Joint Surg.* **11A**, 838–866.

FORLAND M. (1962) Cleido-cranial dysostosis. *Am. J. Med.* **33**, 729–799.

JACKSON W. P. U. (1950) Osteo-dental dysplasia (cleido-cranial dysostosis). *Acta Med. Scand.* **139**, 292–307.

JONES H. W. E. (1937) Cleido-cranial dysostosis. *St Thomas' Hosp. Gaz.* **36**, 193–201.

LASKER G. W. (1946) The inheritance of cleido-cranial dysostosis. *Human Biol.* **18**, 103–126.

MADDOX J. K. (1946) Cranio-cleidal dysostosis. *J. R. Nav. Med. Serv.* **32**, 201–209.

MARIE P. and SAINTON P. (1898) Sur la dysostose cleido-cranienne héréditaire. *Rev. Neurol.* **6**, 835–838. (Cited by Abram, 1907.)

PAYNTON F. J. and DAVIS H. M. (1914) *Proc. R. Soc. Med.* **8**, 21.

SOULE A. B. (1946) Mutational dysostosis (cleido-cranial dysostosis). *J. Bone Joint Surg.* **28A**, 81–102.

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Br. J. Surg. Vol. 66 (1979) 598

Spontaneous rupture of the normal spleen: diagnosis by computerized tomography

DAVID BIRD, M. J. KELLY AND R. N. BAIRD*

> So contrary is it to the established conceptions of pathology, that there are many who doubt that a normal spleen can rupture spontaneously.
>
> Hamilton Bailey (1930)

ATKINSON (1874) described the first case of spontaneous rupture of the normal spleen, and reports of this rare condition appear sporadically. We report here a case which was diagnosed preoperatively by computerized tomography (CT).

Case report

A 55-year-old housewife presented in December 1977 with a 3-week history of left hypochondrial pain of acute onset, which radiated to the back and left groin. She said there was a 'cricket ball' under her left lower ribs. Apart from minor urinary complaints there were no other symptoms. On this and subsequent occasions no history of trauma, however minor, was elicited. On examination there was a fixed, non-tender mass beneath the lower left ribs which was at this stage thought to arise from the left kidney or the spleen.

Investigations showed that haemoglobin, white blood count, platelets, urea and electrolytes, liver function tests, urine and chest X-ray were normal. A soft tissue mass was seen on the plain abdominal X-ray and excretion urography showed medial displacement of the left kidney. A ^{99}Tc^{m} colloid liver and spleen scan was interpreted as normal. CT scanning showed 'a high-lying left kidney, beneath which was an enlarged spleen, the lateral part of which had a different absorption coefficient (i.e. appeared darker) suggesting a lateral subcapsular splenic haematoma' (*Fig.* 1).

Laparotomy confirmed these findings and the spleen, which contained a cricket-ball-sized subcapsular haematoma, was removed. Recovery was uneventful, and histological examination of the spleen showed no intrinsic abnormality. Subsequent review of the isotope scan suggested concavity of the lateral surface of the spleen, but the appearances had not previously been considered diagnostic.

Comment

The existence of such a condition as spontaneous rupture of the normal spleen has been denied. Orloff and Peskin (1958) reviewed 71 cases of alleged spontaneous rupture of the normal spleen and found that possible causes had not been excluded in 43 cases (61 per cent). However, in the absence of a history of trauma, perisplenic adhesions or abnormalities of the spleen, a case such as ours appears, as far as it is possible to ascertain, to be truly spontaneous.

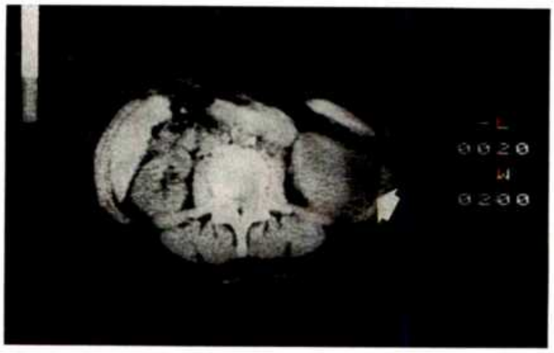

Fig. 1. Computerized tomography scan showing subcapsular splenic haematoma.

In the diagnosis of subacute splenic rupture ^{99}Tc^{m} colloid liver and spleen scanning may be unreliable (Budd et al., 1976), being unable to demonstrate defects smaller than 2 cm in diameter, or to demonstrate perisplenic structures including subcapsular haematoma of the spleen. Selective arteriography has been shown to be more accurate (Drapanas et al., 1969) but is a highly skilled invasive technique not without morbidity. In the present case the diagnosis was established by CT scanning, which we suggest may quickly and non-invasively provide valuable information in the investigation of suspected subcapsular splenic haematoma and thus lead to earlier definitive surgery.

References

ATKINSON E. (1874) Death from idiopathic rupture of the spleen. *Br. Med. J.* **2**, 403–404.

BAILEY H. (1930) Spontaneous rupture of the normal spleen. *Br. J. Surg.* **17**, 417–421.

BUDD D. C., FOUTY W. J. et al. (1976) Occult rupture of the spleen: a dilemma in diagnosis. *JAMA* **236**, 2884–2886.

DRAPANAS T., YATES A. J., BRICKMAN R. et al. (1969) The syndrome of occult rupture of the spleen. *Arch. Surg.* **99**, 298–306.

ORLOFF M. J. and PESKIN G. W. (1958) Spontaneous rupture of the spleen: a surgical enigma. *Int. Abstr. Surg.* **106**, 1–11.

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Correspondence

Effect of levamisole on postoperative immunosuppression

Sir,

Cell mediated immunity is depressed following surgery (Cochran et al., 1972; Slade et al., 1975). A reduced lymphocyte responsiveness to phytohaemagglutinin (PHA) has been demonstrated in the first days after operation and this usually lasts 2–4 weeks (Roth et al., 1976). Immunodepression could conceivably contribute to the risk of metastatic diffusion and/or infections.

Our purpose was to determine whether levamisole, an orally effective modifier of the immune response (Tripodi et al., 1973), was able to reverse postoperative immunodepression.

In our study, based on 22 immunodepressed cancer patients, the lymphocyte response to PHA was evaluated 3 days (T_{-3}) and just before (T_0) operation and 2 (T_2), 4 (T_4) and 14 (T_{14}) days after operation. Eleven patients received one dose of 150 mg levamisole orally daily for 3 days between T_{-3} and T_0, and 11 patients were controls.

The results are summarized in the Table. In levamisole pretreated patients the lymphocyte response to PHA at times T_4 and T_{14} appears to be greatly increased compared with preoperative values. Furthermore, lymphocyte reactivity 4 and 14 days after surgery is significantly higher in treated than in control patients.

	LT	CO
T_{-3}	$4{\cdot}42 \pm 3{\cdot}75$	$2{\cdot}82 \pm 1{\cdot}60$
T_0	$2{\cdot}72 \pm 2{\cdot}19$	$2{\cdot}61 \pm 1{\cdot}13$
T_2	$2{\cdot}45 \pm 1{\cdot}55$	$1{\cdot}95 \pm 0{\cdot}53$
T_4	$5{\cdot}89 \pm 3{\cdot}32$*	$3{\cdot}29 \pm 1{\cdot}10$
T_{14}	$8{\cdot}44 \pm 4{\cdot}64$**	$3{\cdot}43 \pm 1{\cdot}86$

LT, Levamisole treated; CO, controls. Values are stimulation index $\bar{x} \pm$ s.d. Stimulation index = (mean count/min PHA stimulated cultures)/(mean count/min unstimulated cell cultures). Normal values >5.
* $P < 0{\cdot}02$ for T_0 *v.* T_4. ** $P < 0{\cdot}005$ for T_0 *v.* T_{14}.

Our data seem to agree with those of Windle et al. (1978), confirming that levamisole could reverse postoperative immunodepression. This may be of some importance in preventing early septic complications in postoperative care and cancer cell dissemination after a surgical procedure.

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COCHRAN A. J., SPLIG W. J. S., MACKIE R. M. et al. (1972) Postoperative depression of tumour-directed cell-mediated immunity in patients with malignant disease. *Br. Med. J.* **4**, 67–70.

ROTH J. A., GOLUB S. H., GRIMM E. A. et al. (1976) Effect of operation on immune response in cancer patients: sequential evaluation of in vitro lymphocyte function. *Surgery* **79**, 46–51.

SLADE M. S., SIMMONS R. L., YUNIS E. et al. (1975) Immunodepression of major surgery in normal patients. *Surgery* **78**, 363–372.

TRIPODI D., PARKS L. C. and BRUGMANS J. (1973) Drug-induced restoration of cutaneous delayed hypersensitivity in anergic patients with cancer. *N. Engl. J. Med.* **289**, 354–357.

WINDLE R., WOOD R. F. M. and BELL P. R. F. (1978) Reduction of the duration of postoperative immunosuppression by levamisole. *Br. J. Surg.* **65**, 355.

Talc on surgeons' gloves

Sir,

We would like to correct a misconception which appears to have arisen from our original paper in your journal entitled 'Identification of talc on surgeons' gloves and in tissue from starch granulomas', **62**, 941–944. Two subsequent papers in your journal, namely 'The significance of starch powder contamination in the aetiology of peritoneal adhesions' (Cooke and Hamilton, **64**, 410–412) and 'Talc granuloma of the ureter: a case report' (Joannides, **65**, 883–885) have both drawn an incorrect conclusion from our paper. It has been suggested that we reported that talc contamination occurs during the preparation of Bio-sorb. We have examined numerous sachets of Bio-sorb which are included with the surgeons' gloves and also samples from bulk material which would be used as a dusting powder for releasing the rubber gloves from their moulds; in none of these samples have we encountered talc. The talc particles which were identified on the surface of the UK-manufactured surgeons' gloves were from accidental contamination, which has now been corrected. The large number of talc particles observed on certain American-produced surgeons' gloves, on occasions in excess of 6×10^7 particles/cm^2, would suggest that it is this material that is being employed as the releasing dusting powder in the moulding process.

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Book reviews

Radiologic Management of the Massively Traumatized Patient

Ayella. 280 × 220 mm. Pp. 297 + xvi, with 612 illustrations. 1978. Baltimore: Williams & Wilkins. $50.00.

Dr Ayella has put all those concerned with the care of the severely injured in his debt by producing this book, of which he has written 13 of the 16 chapters. The other three deal with computed tomography, ultrasound and nuclear medical methods of investigation. Apart from explaining in clinically well-informed, as well as radiological, detail a very wide range of methods of investigation, the author is at pains repeatedly to point out the dangers of unthinking resort to radiological investigation. In emphasizing the need to be content in many cases with rather poor portable films he also indicates how best to make use of what information is made available and what needs to be done to avoid errors of omission.

The fifteenth chapter on the extremities makes rather disappointing reading after the previous fourteen. It has few headings and omits a number of areas and subjects that are well-known causes of difficulty and confusion. In future editions I would like to see this section expanded and contain more advice about how to diagnose in good time the 'minor' injuries that may give the survivor of severe injuries his main lasting complaints.

The book is well produced but there are a few spelling mistakes, especially Le Forte, Fig. 15.119 is upside down and some of the X-ray films are of surprisingly poor quality.

P. S. LONDON

Operative Surgery

General Editors Charles Rob and Sir Rodney Smith. Third edition.

Accident Surgery

Edited Peter London. 282 × 220 mm. Pp. 600. Illustrated. 1978. Sevenoaks: Butterworths. £55·00.

One difficulty which faces the editors of all practical books on operative surgery is especially troublesome for the editor of a book on accident surgery. How to give sufficient detail to permit effective understanding of the principles and techniques of the operations, and yet not overcrowd the book with text and pictures so that it becomes a vast and unwieldy tome. This difficulty has been successfully surmounted by Mr Peter London in this volume on accident surgery in the *Operative Surgery* series. It is good to see a book so arranged that adequate information is displayed in a simple and uncomplicated fashion so that advice is easily available.

The many international contributors have produced a well-balanced book yet each chapter is sufficiently different in content and illustration to make refreshing reading for the trainee using the volume as a textbook of accident surgery.

Despite the general high standard of the text and illustrations, some sections do not entirely satisfy. The section on exposure of the arteries is obviously not written specifically for this book, and it is difficult to find advice in the section on the management of many common problems encountered in arterial trauma. I did wonder too if this book was the place for a discussion on the merits of single-layer gut anastomosis.

The section on liver injury is particularly good. It gives a very well-balanced view of the problem and provides advice and guidance on all aspects of this difficult and formidable injury.

This book fulfils a need long felt in accident departments and certainly should be available for reference in any operation theatre where major trauma is treated. It is sad that its price, like that of the other volumes in this series, puts the book virtually out of reach of most trainees, but nevertheless it is still worth the money.

H. JOHN

Lumbar Puncture and Spinal Analgesia

J. A. Lee and R. S. Atkinson. 222 × 145 mm. Pp. 214, with 108 illustrations. 1978. Edinburgh: Churchill Livingstone.

Some doctors believe that a medical anaesthetist is essential for successful surgery. Most anaesthetists like to think so, anyway. In fact, in large areas of the world, they are a luxury and anaesthesia may have to be administered by assistants or by the surgeon himself. In such circumstances, the value of a thorough, practical grasp of the technique of spinal analgesia is self-evident.

In the UK spinal and epidural anaesthesia are under-utilized in routine anaesthetic practice. This is due, in part, to the Woolley and Roe tragedies and, in part, to the great advance in general anaesthesia which followed the introduction of muscle relaxants. However, the principal bar to these techniques is the fact that they require more time in the anaesthetic room. It is in this context that one can unhesitatingly recommend this book to surgeons, for there is no doubt that it is when the surgeon appreciates the value to him of these techniques that any inconvenience caused by their employment is outweighed by their benefits. These benefits range from a reduction in bleeding, good relaxation and contracted gut, to better postoperative analgesia. This book shows how the benefits may be maximized and the disadvantages minimized.

Only a couple of pages are specifically directed at the single-handed surgeon: the remainder is clearly written for anaesthetists. And it is indeed clearly written—and clearly illustrated, attractively printed and carefully referenced. In consequence, the surgeon contemplating undertaking spinal anaesthesia could hardly find a better primer to set him on the right road. Surgeons working in the lower abdomen or on the legs should also be stimulated to try the influence of this type of anaesthesia on their practice.

M. D. VICKERS

Ancient Indian Surgery

Diagnostic Considerations, Volume 3

Edited G. D. Singhal, L. M. Singh and K. P. Singh 140 × 215 mm. Pp. 264 + xxiv. 1972. Allahabad, India: Singhal Publications.

Anatomical and Obstetric Considerations, Volume 4

Edited G. D. Singhal and L. V. Guru. 140 × 225 mm. Pp. 241 + L. 1973. Allahabad, India: Singhal Publications.

Toxicological Considerations, Volume 7

Edited G. D. Singhal and R. N. Dwivedi. 135 × 220 mm. Pp. 226 + xL. 1976. Allahabad, India: Singhal Publications.

A look into the past can occasionally make a welcome change in an era when reports on double blind trials and the like are numerous and only occasionally relieve the blindess of ignorance.

These three books, part of a series dealing with diagnosis, anatomy and toxicology, are a credit to the editor-in-chief, Dr G. D. Singhal of the Department of Paediatric Surgery at Banares University and his several co-editors. This English translation from Sanskrit of the great treatise of *Susruta Samhita*, a famous ancient Indian surgeon, presents an authentic scientific version of this outstanding classic.

Many subjects are covered including burns, lithotomy, piles, fistula, skin and eye diseases and are claimed by the editor to antedate many of the well-known classical descriptions.

It is a fascinating work and a valuable contribution towards our knowledge of world medical history. It is also a readable book with a compelling charm, especially so to those who have a first-hand knowledge of the Indian subcontinent. I personally enjoyed reading it.

G. J. HADFIELD

Recently Published

QUESTIONS AND ANSWERS IN GENERAL SURGERY

H. P. HENDERSON, FRCS, *Senior Registrar, Plastic and Jaw Surgery, Fulwood Hospital, Sheffield;* and M. J. KELLY, MChir, FRCS, MRCP, *Senior Registrar in General Surgery, Bristol Royal Infirmary*

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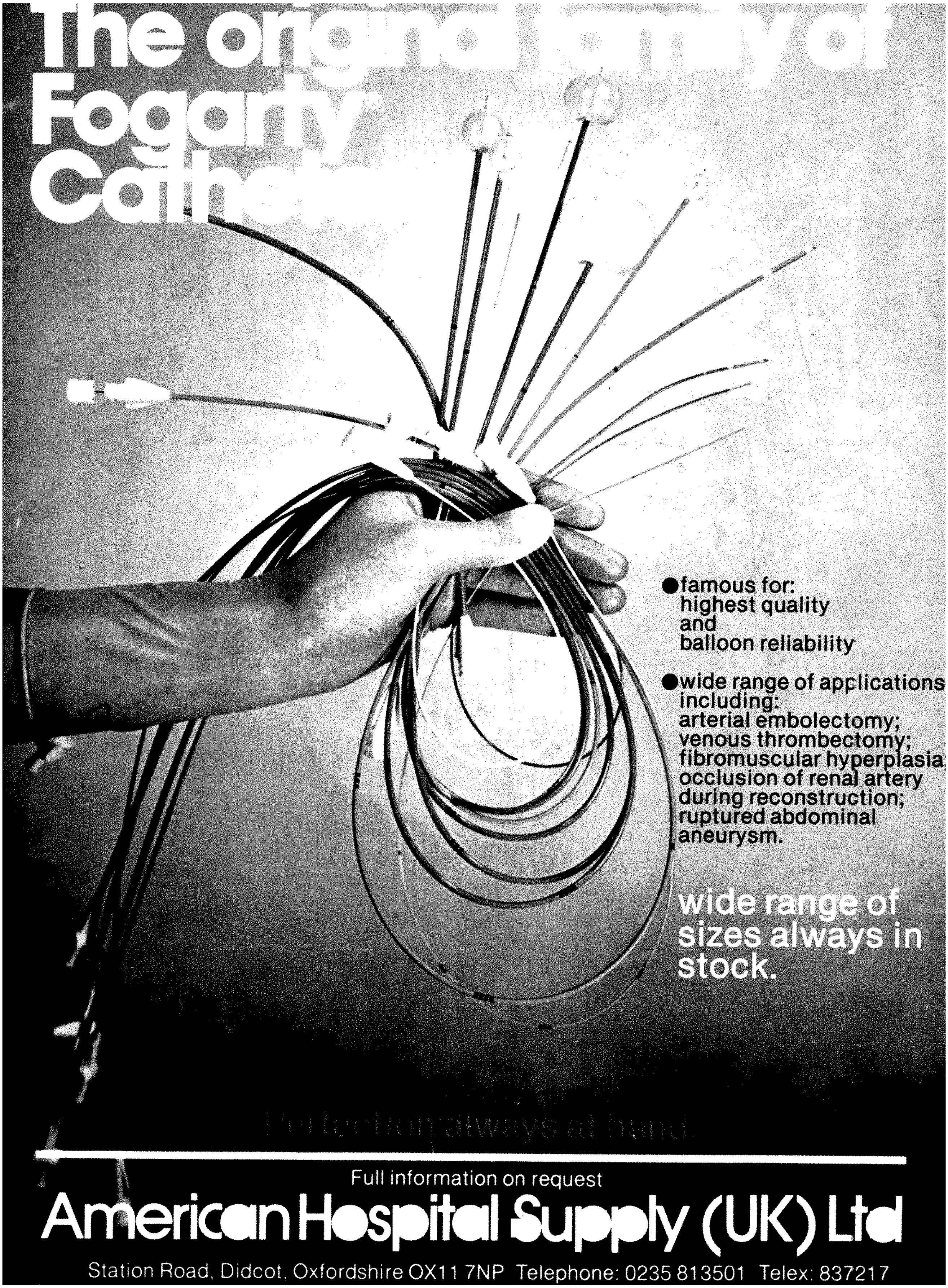

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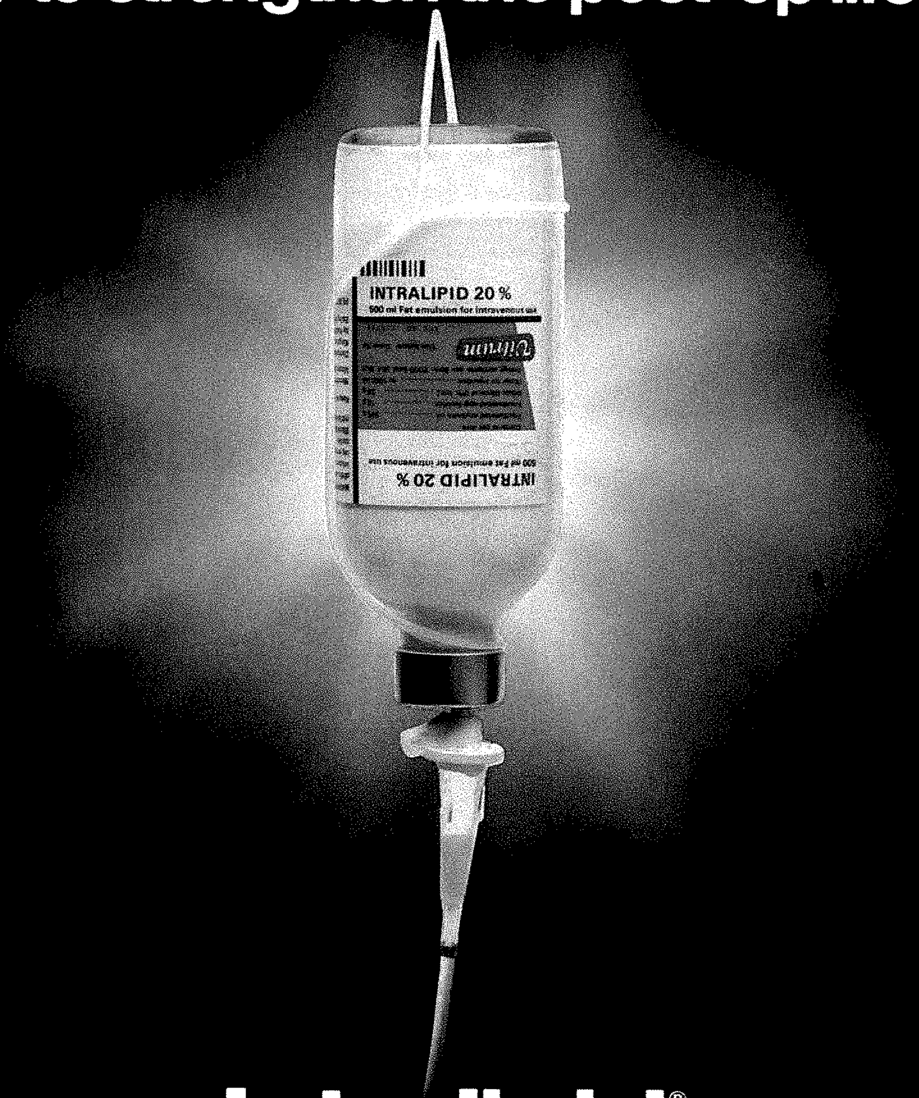
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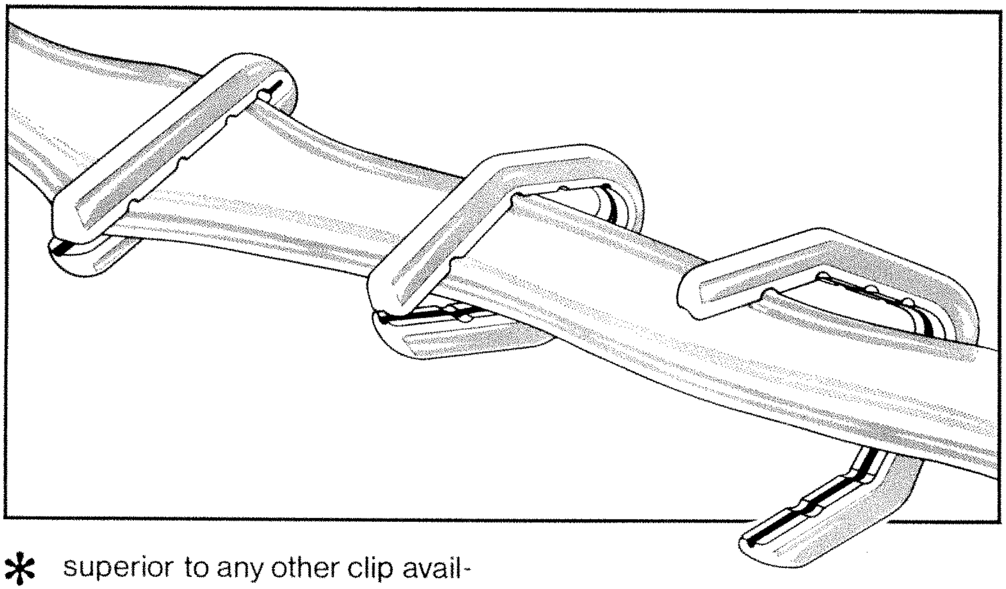

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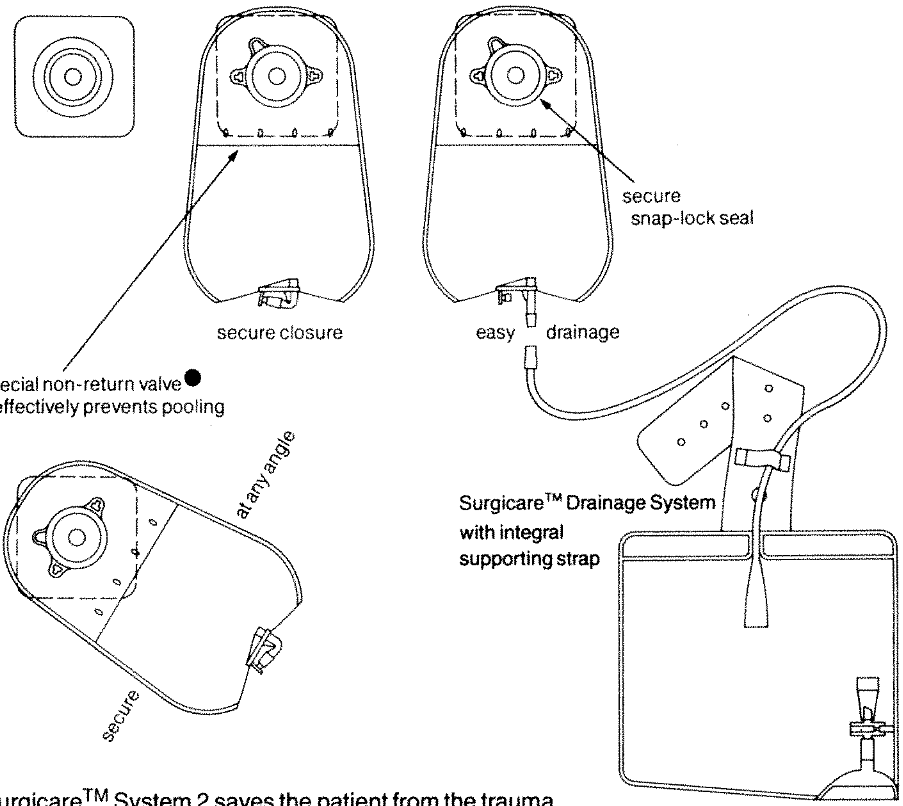
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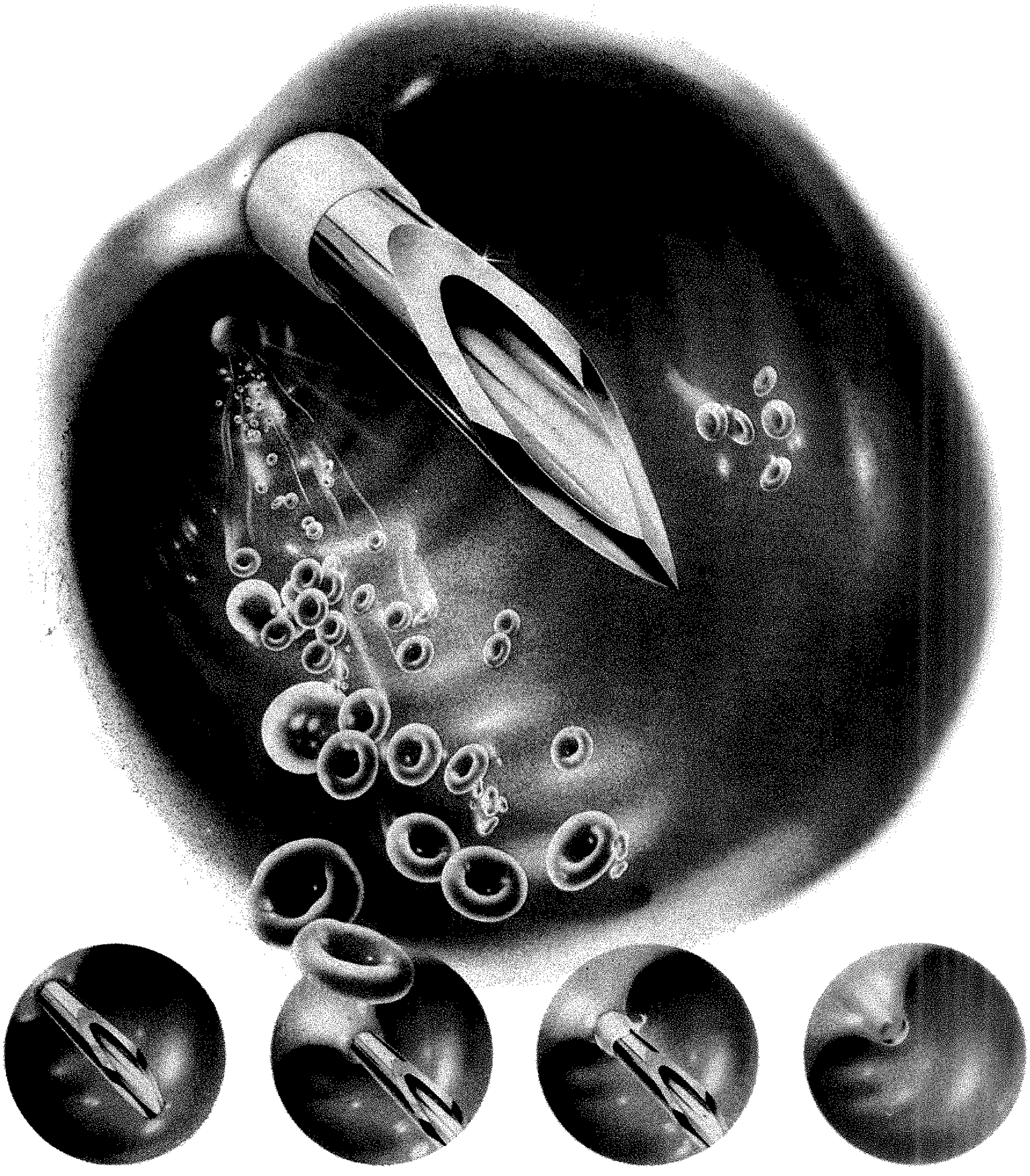

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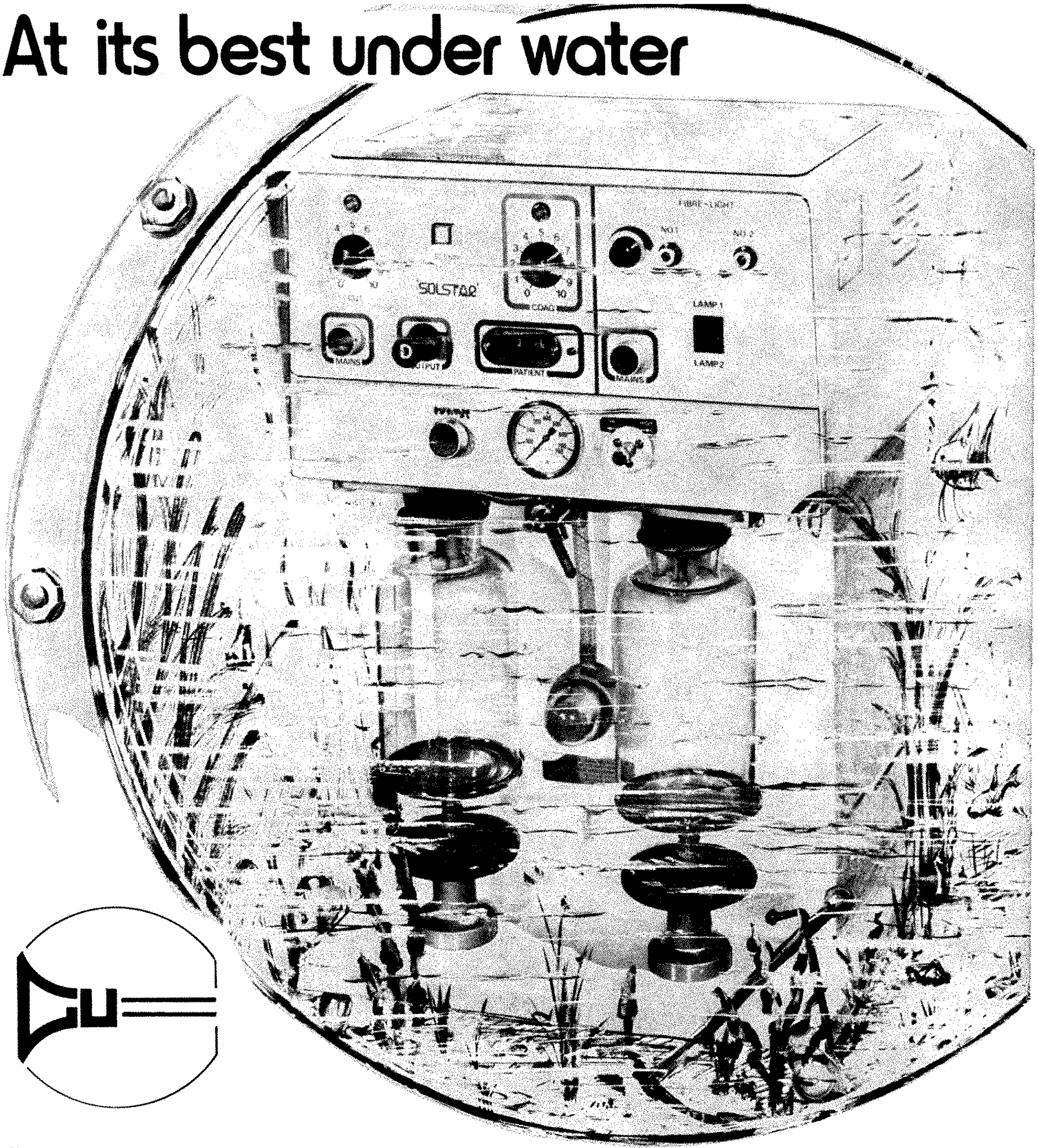

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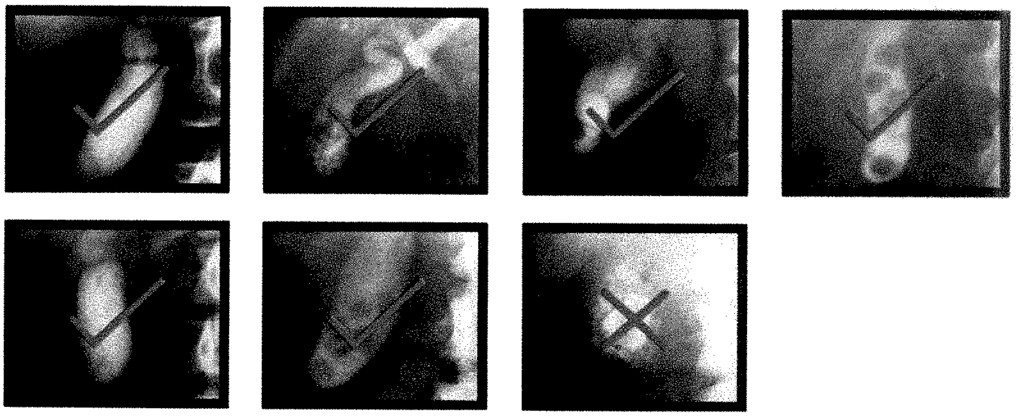

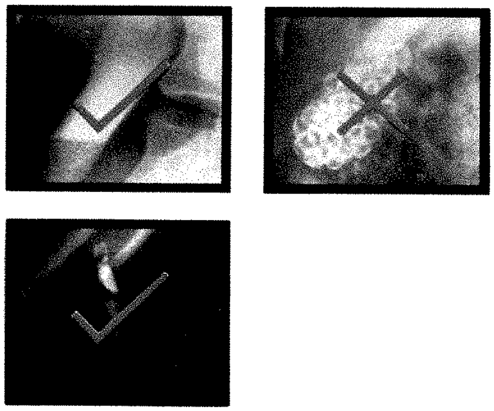

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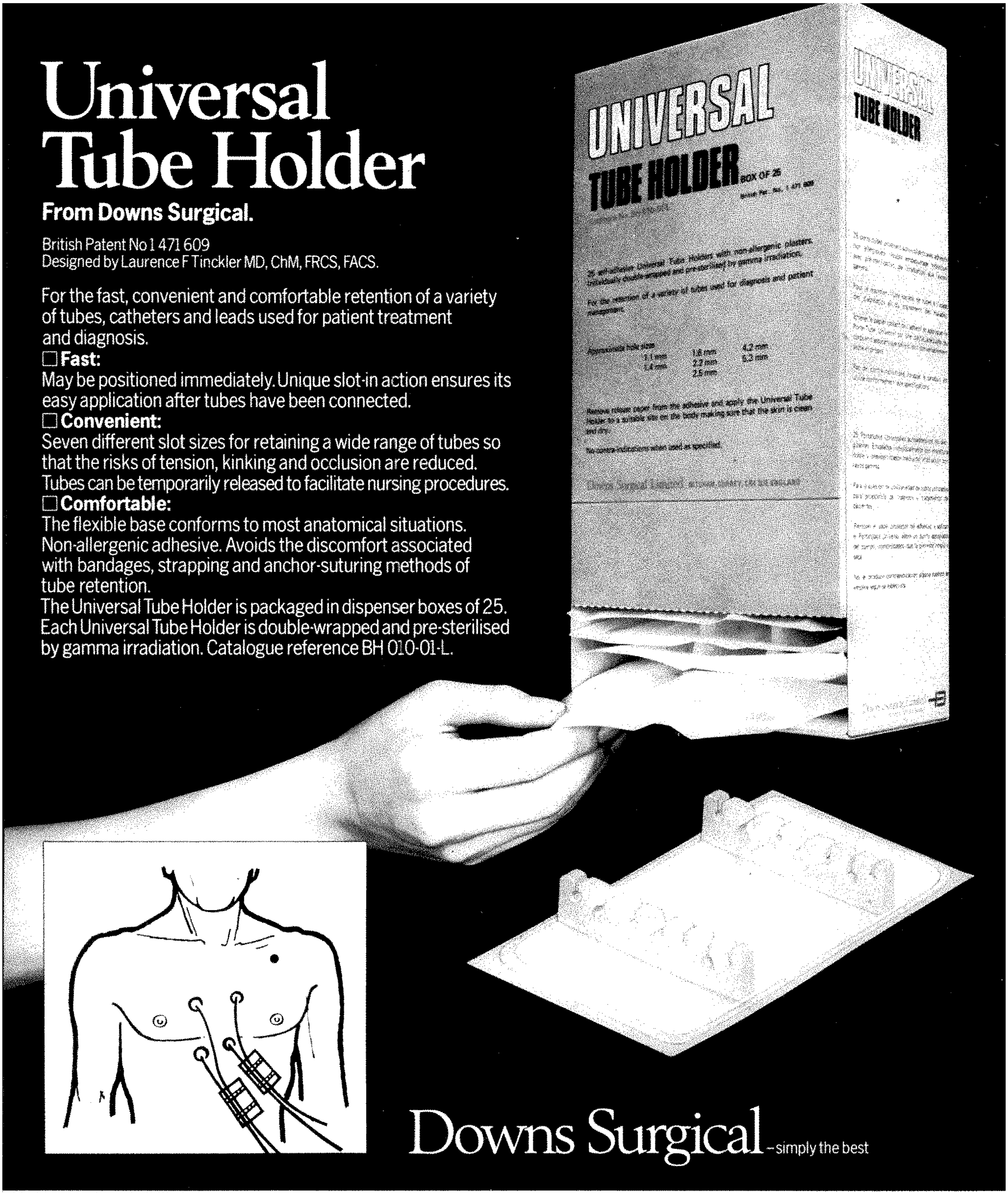
2. Thistle, J. L., Hofmann, A. F., Ott, B. J. and Yu, P. Y. S. (1976) Gallstone dissolution with chenodeoxycholic acid 1969–1976. The Mayo Clinic Studies. Gastroenterology 70, 943 (abstract)



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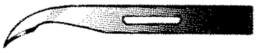

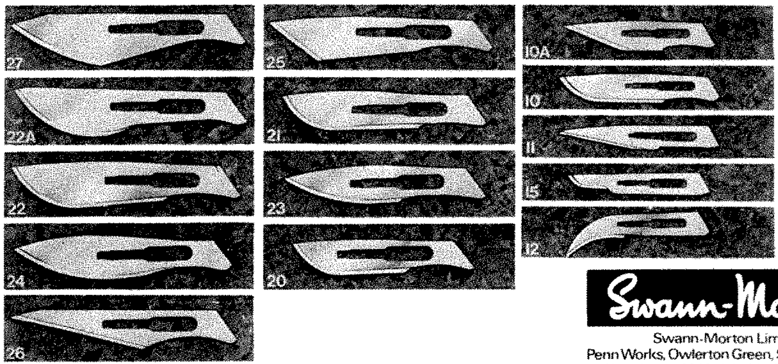

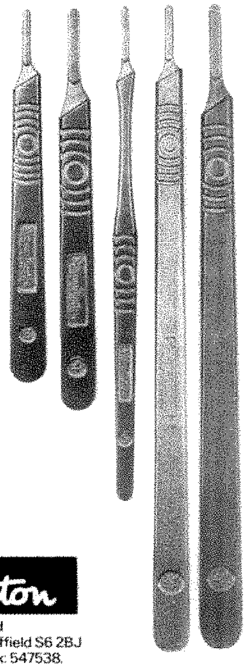

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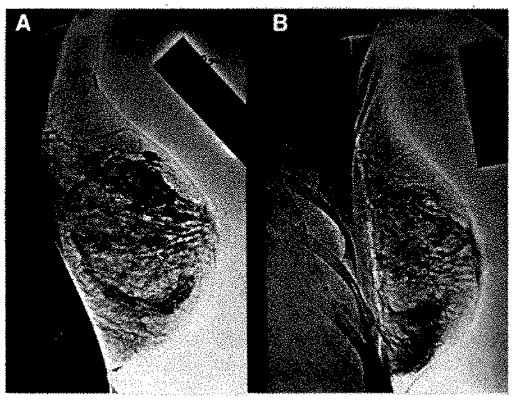

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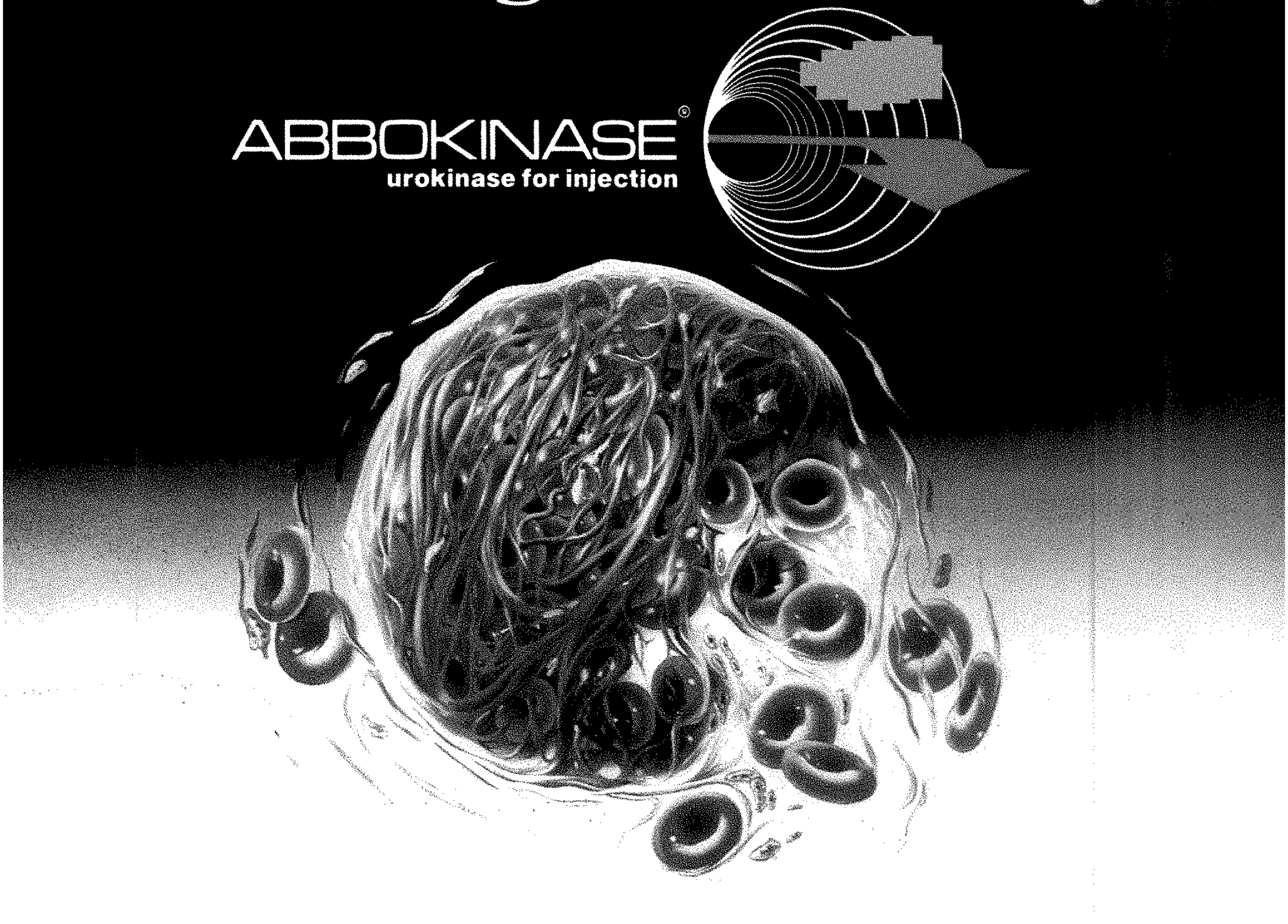

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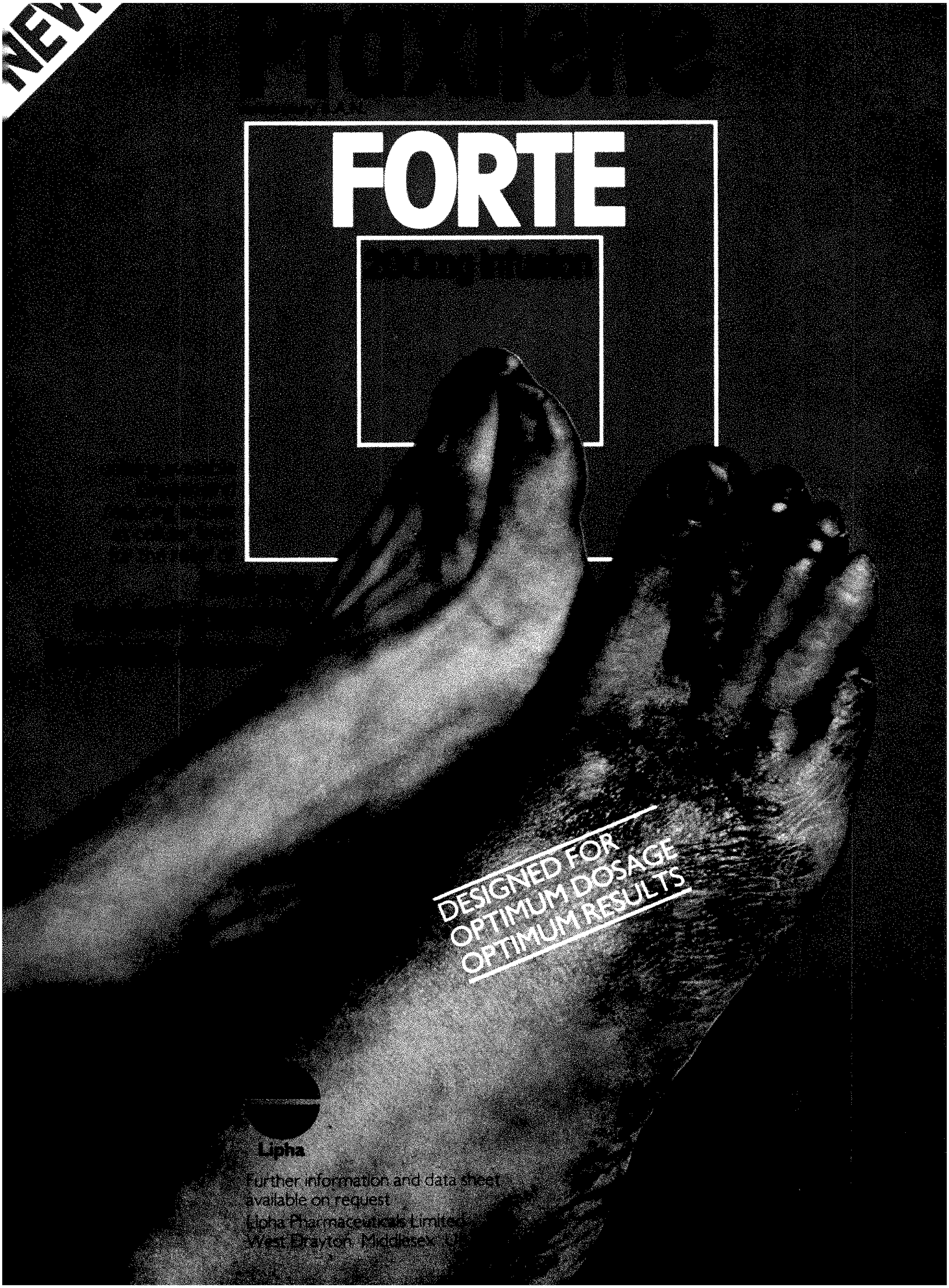
Kakkar V.V, Scully M.F: *Op. cit.*, p 192. 3. Genton E, Claman H.N: Urokinase: antigenic studies in patients following thrombolytic therapy. *J. Lab. Clin. Med.* **15**: 619, 1970. 4. Urokinase Pulmonary Embolism Trial: Phase I results: a cooperative study. *JAMA* **214**: 2163, 1970. 5. Urokinase Pulmonary Embolism Trial Study Group: Urokinase-streptokinase Embolism Trial. *JAMA* **229**: 1606, 1974. Further information available on request from Abbott Laboratories Limited, Queenborough, Kent ME11 5EL. ®Registered Trade Mark of Abbott Laboratories Ltd. AK389.



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The British Journal of Surgery

Vol. 66 : No. 9 : September 1979

Br. J. Surg. Vol. 66 (1979) 601-606

Rupture of the abdominal oesophagus: a review

P. V. WALSH*

SUMMARY

'Spontaneous' rupture of the oesophagus usually affects the lower third, less commonly the middle third and rarely the cervical oesophagus. Rupture limited to the intra-abdominal oesophagus is rare. Such a case is described here and previously reported cases are reviewed. Vomiting-induced gastro-oesophageal injuries and their aetiology are discussed and the management of spontaneous rupture is reviewed.

Case report

A 58-year-old business executive developed diarrhoea and vomiting the day after returning from abroad. He vomited nine or ten times that evening and experienced epigastric pain. Four hours later the pain suddenly became severe and radiated to the right hypochondrium, and retrosternally. The patient was sweating, dyspnoeic and hypotensive with a bradycardia (60/min).

A diagnosis of myocardial infarction was made by the patient's GP and he was admitted to a medical ward. He was dehydrated, confused and restless with intractable pain, but he was by now normotensive. His lung fields were clinically clear, his abdomen rigid and tender, with a succussion splash.

Investigations showed Hb 17·5 g/dl, WBC 14×10^9/l, normal urea, electrolytes and amylase and a normal ECG. Portable chest X-ray showed a normal mediastinal outline and clear lung fields. Abdominal X-rays did not show free intraperitoneal gas. None the less, a diagnosis was made of a perforated intra-abdominal viscus. Peritoneal lavage yielded a faintly sanguineous fluid, with normal amylase concentration. Ten hours after perforation, laparotomy was performed through a right upper paramedian incision. The only abnormal findings were a haematoma around the cardia of the stomach and into the gastrohepatic omentum, and surgical emphysema along the lesser curve of the stomach. At this juncture, a fibreoptic gastroscope was passed from above, demonstrating a longitudinal mucosal tear on the anterior wall of the oesophagus, just above the oesophagogastric junction. The laparotomy was resumed. The peritoneum was incised at the cardia and a 1-cm vertical perforation of the muscle layer of the oesophagus was found communicating with the lumen. Soiling was negligible. The perforation was closed with interrupted chromic catgut sutures and then covered with a wrap-over of anterior stomach wall. An intubated jejunostomy was fashioned and two wide-bore fenestrated tube drains were placed to the left subphrenic space and along the lesser curve to the cardia. The nasogastric tube was positioned at the antrum. The peritoneal cavity was irrigated with noxythiolin.

Antibiotic treatment was started peroperatively with gentamicin and immediately postoperatively with clindamycin and ampicillin. Artificial ventilation was required to maintain satisfactory blood gases. Culture swabs taken at operation yielded a growth of *Streptococcus viridans*, *Staphylococcus aureus* and *Klebsiella* spp. Ampicillin was discontinued and cloxacillin commenced. On the seventh day bilateral serous pleural effusions were drained (1·8 l from the right, 0·3 l from the left). Gram stain showed no organisms and culture was negative. The effusions did not reaccumulate. Culture swabs taken from the abdominal tube drains on the seventh day yielded a growth of klebsiella sensitive to gentamicin. Tracheostomy was performed on the eighth day. The patient became jaundiced, with a markedly raised direct bilirubin, and his condition deteriorated. Gentamicin was changed to tobramycin and both clindamycin and cloxacillin were stopped on the twelfth day. Leucocytosis and pyrexia suggested intra-abdominal sepsis, so a repeat laparotomy was performed on the fourteenth day. The liver was enlarged, but no hepatic abscess was detected. Collections of pus were found beneath the left lobe of the liver (30–40 ml) and just above the oesophageal hiatus, in the right side of the mediastinum (20 ml). The oesophageal repair was intact and was not disturbed. There was no extrahepatic biliary obstruction and a liver biopsy showed centrilobular congestion with bile thrombi and some liver cell damage. Pus swabs grew *Pseudomonas aeruginosa* and *Klebsiella* spp., both sensitive to gentamicin and tobramycin.

Postoperatively there was a temporary improvement in the patient's condition. Blood cultures were sterile. After consultation with the bacteriologist, tobramycin was changed to amikacin on the twenty-second day Despite intensive support —respiratory, cardiovascular, nutritional (intravenous and enteral) and antibacterial—his condition deteriorated and he died on the twenty-eighth day. Permission for post-mortem examination was refused.

'Spontaneous' injuries of the oesophagus and stomach

The term 'spontaneous' implies injuries produced by vomiting, and excludes those caused by external trauma and instrumentation. It also excludes those cases where there is an obvious mural cause of rupture such as a carcinoma of the oesophagus. Truly spontaneous 'out of the blue' ruptures must be exceedingly rare. The terminology has been debated before, and such alternative names as post-emetic, emetogenic and barogenic have been proposed. 'The deadliest rupture' (Penka et al., 1977) is a graphic but discouraging term, and 'Boerhaave's syndrome' remains a useful heading under which to approach the management of 'spontaneous rupture'. Whether the oesophagus which is normal in every respect can rupture spontaneously, as Barrett (1946) postulated, will not be debated here, but many cases are associated with some abnormality, especially hiatus hernia.

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While rupture is usually induced by vomiting, it can complicate defaecation, epileptic convulsion, parturition, forceful swallowing or laughing (Triggiani and Belsey, 1977).

It is not only the oesophagus that can rupture, however, and Watts (1976) reviewed the literature to find 5 cases of rupture of the stomach caused by vomiting in the absence of other factors such as pyloric stenosis or a mixture of champagne and sodium bicarbonate (Bruno et al., 1963) which cause gastric distension. He found that gastric overdistension commonly produces lesser curvature ruptures, whereas vomiting produces a perforation high on the greater curvature or fundus. He concluded that the vomit-induced rupture occurred while the stomach was in the chest and he attributed the positioning of the rupture to the concurrent presence of a hiatus hernia. He also observed that the mucosal laceration of the Mallory–Weiss syndrome was commonly found in the stomach when a hiatus hernia was present, and in the oesophagus when there was no hernia. Stilwell (1978) recently reported a further case of intrathoracic rupture of a hiatus hernia in a 70-year-old woman who was admitted with a strangulated femoral hernia.

The mucosal laceration of the Mallory–Weiss syndrome can, as stated, occur in the stomach or in the oesophagus. Usually, the haemorrhage is self-limiting, but blood loss may be heavy, and 5 of the 21 cases originally described by Mallory and Weiss bled to death. Sometimes the bleeding point may be accessible through a gastrotomy but clearly it will not be so easily exposed if it is in the oesophagus. Atkinson and his colleagues (1961) reported 11 patients with mucosal tears at the oesophagogastric junction. Only 5 of these were cases of typical Mallory–Weiss syndrome, and there was one case of truly spontaneous tear, and one case each of tear induced by epilepsy, asthma and coughing. The tears were longitudinal, up to 3·5 cm long and 1·4 cm wide, frequently multiple and situated above, below, or across the cardia, anterior or posterior. It has been stated (Holmes, 1966) that Mallory–Weiss syndrome and Boerhaave's syndrome are not different forms of the same condition since there are anatomical, pathological and clinical differences between the two lesions. Zikria et al. (1965), however, described a case of Mallory–Weiss syndrome who continued vomiting after admission and developed a perforation of the oesophagus. Van de Velde and his colleagues (1976) and Bruno and his colleagues (1963) have reported cases of full-thickness rupture with coexistent separate mucosal tear. The attachment of a label of 'Mallory–Weiss syndrome' should not lull the clinician into complacency about the management of a case of haematemesis. Furthermore, haematemesis from duodenal ulcer (Zikria et al., 1965; Callaghan, 1972) and oesophageal varices (van de Velde et al., 1976) have been complicated by oesophageal perforation.

Interstitial haemorrhage in the lower oesophagus caused by vomiting with the production of a submucosal haematoma has been described, under the heading 'oesophageal apoplexy' (Smith et al., 1974). Of the three elderly ladies described (aged 60, 61 and 66) two had a sliding hiatus hernia and the third gave a long history of dyspepsia and heartburn. All developed the haematoma on the posterior wall of the lower oesophagus and presented with pain and dysphagia. All recovered fully on conservative management.

Kelley et al. (1972) described an intramural perforation in a 21-year-old man who developed dysphagia as he was recovering from a respiratory tract infection with coughing and sneezing. He vomited 10 ml of blood and then experienced substernal pain. Barium swallow showed narrowing of the lumen of the mid-oesophagus with some extraluminal barium. Oesophagoscopy showed a 15-mm tear in the mucosa of the mid-oesophagus on the posterior wall. He was treated conservatively until, after 2 weeks, his dysphagia worsened. Repeat endoscopy revealed the tear as before, with a 4-cm submucosal track leading from it. In view of the danger of perforation developing, right thoracotomy was performed but there was no apparent external abnormality of the oesophagus. It is possible that this patient developed a haematoma, as a result of coughing and sneezing, and that this caused his dysphagia. Rupture of the haematoma into the lumen would cause him to 'vomit' the 10 ml of blood described, leaving a haematoma cavity, rather like the ones described by Smith and his colleagues (1974), though a few centimetres higher in the oesophagus.

The conditions outlined so far form an interesting spectrum of injuries.

Boerhaave's syndrome—full-thickness rupture of the oesophagus—may occur at any level. The laceration is nearly always vertical but may rarely be transverse, as in the first reported case, that of the unfortunate Baron de Wassanaer, whose oesophagus disrupted completely. There may rarely be multiple perforations (Van de Velde et al., 1976). The perforation may measure anything up to 10 cm long but is usually of the order of 6 cm in length. It is most common in the lower third, just above the diaphragm, 80–90 per cent being on the left side, and perforation into the left pleural cavity has usually taken place by the time of admission. Rupture in the middle third is more commonly on the right side (6 out of the 9 cases reviewed by Holt et al., 1978). Most series show a male preponderance. Barrett (1946) quoted Walker's 1914 series of 22, all but 2 of whom were male. Mori et al. (1977) found 59 cases in the Japanese literature over a 40-year period and 53 were male. All of the 8 late-diagnosed cases reported by Harrison et al. (1976) were male. Keighley et al. (1972) reported 9 males out of 12 cases over a 20-year period. Triggiani and Belsey (1977), however, found no male preponderance in their 11 cases over a 25-year period. The victim is usually in his fifth or sixth decade, but cases have occurred in infancy, childhood and adolescence.

Rupture not uncommonly occurs in association with a hiatus hernia or below a stricture, though it has been described (Harma et al., 1968) occurring above a stricture. The literature contains many assertions of an association with oesophagitis and there has been one case reported (Habein, 1977) in a 37-year-old man with Ehlers–Danlos syndrome and a small sliding hiatus hernia. There is an increased incidence among chronic alcoholics. Penka et al. (1977) described 5 cases of idiopathic muscular hypertrophy of the oesophagus, 2 of whom suffered spontaneous rupture. The patient presented here had previously complained of mild dysphagia, and, although the oesophagus was endoscopically normal, it is possible that this was an example of mild dysfunction. Perhaps more cases have an unrecognized abnormality of function or structure than are detected.

The pressure required to rupture the cadaveric oesophagus *in situ* has been measured (Tidman and John, 1967) and a mean figure of 4·6 lb/in^2 produced a tear averaging 2·7 cm in length. Twelve of the fifteen tears were on the left of the lower third, just above the diaphragm, while the remaining three were on the right just below the azygos vein. The authors concluded that the upper end of the oesophagus must be occluded to permit such a pressure to be achieved.

The usual explanation for the site of rupture is that the oesophageal wall is unsupported on the left in the lower third and on the right in the middle third. Edwards (1969) observed that during barium examinations under fluoroscopy, patients who demonstrated a small hiatus hernia on the antigravity film also produced a hernia when they retched. This observation suggests that under conditions of sudden forceful vomiting, such patients would herniate the stomach into the chest and perhaps create a redundant 'loop' of oesophagus in the lower mediastinum. Patients with an overt sliding hiatus hernia presumably herniate maximally during the increased intra-abdominal pressure of vomiting to produce a redundant loop. If this 'loop' kinks, it would occlude the lumen and provide the closed viscus that Tidman and John (1967) imply is necessary for rupture to occur. If kinking occurs low in the oesophagus, the lower third will rupture. If the kink occurs around the azygos vein, the middle third will rupture, the rupture in each case occurring on the convex side of the loop —left in the lower third, right in the mid-third.

Spontaneous rupture of the cervical oesophagus is rare. Russell and MacDonald (1968) reviewed the condition when the first case, reported by Russell in 1953, presented again after 26 years with a further very small perforation in the cervical oesophagus. The patient gave a long history of mild dysphagia for solids and, on endoscopy, the cricopharyngeus was noted to be tight. The authors found one other reported case, also with a minute perforation, which was treated conservatively. Mori et al. (1977) found only 2 reported cases of spontaneous upper oesophageal rupture in their review of the Japanese literature over 40 years.

Intra-abdominal 'spontaneous' perforation of the oesophagus

There are very few recorded cases of spontaneous rupture limited to the intra-abdominal portion of the oesophagus and without involvement of, and extension into, the pleural spaces.

The first recorded, and often quoted, case was an intraperitoneal perforation in a woman in her early twenties (Sencert, 1911). She had several months' history of postprandial abdominal pain relieved by vomiting. Suddenly, one afternoon, while she was sitting reading, her oesophagus perforated. At laparotomy she was found to have generalized peritonitis and a perforation 'the size of a 50 centime piece' in the oesophagus, 2 cm above the cardia. Macroscopically, this was a chronic ulcer, and it was repaired using a wrap-over of gastric fundus. The patient survived. This was an unusual condition, but the rupture was not spontaneous.

Thornley and Wallwork (1978) reported an apparently vomiting-induced intraperitoneal perforation in a 30-year-old woman. The condition was remarkably benign and 4 weeks elapsed before the patient sought attention for her left-sided chest and shoulder pain. Laparotomy showed a 2-mm perforation in the anterior wall of the oesophagus near the cardia. The patient survived. The case appears to be unique.

Triggiani and Belsey (1977) had 1 case of intra-abdominal rupture in their series of 11 cases over 25 years. It is presumably the same case that had a pneumoperitoneum, implying intraperitoneal rupture, but no further account is given of the case, and no indication is given as to whether the rupture in this case was entirely intra-abdominal.

Bruno and his colleagues (1963) reported a case of rupture extending for 5 cm in the posterior wall of the oesophagus and extending for 1·5 cm into the posterior wall of the stomach. The patient had mediastinitis, gas under both diaphragms on X-ray and subcutaneous emphysema in the right supraclavicular fossa. At laparotomy 'there was no evident perforation into the peritoneal cavity', and gastrotomy merely showed blood 'oozing from the mucosa of the entire stomach'. It is not clear whether the subdiaphragmatic gas was intra- or extraperitoneal. Subdiaphragmatic gas is unusual but the literature contains several reported cases of oesophageal rupture extending into the stomach. Air could enter the peritoneal cavity if an oesophageal rupture extended into the peritonealized surface of the stomach or oesophagus.

Strauch and Lynch (1965) reported the first recorded case of spontaneous, subphrenic, extrathoracic rupture of the oesophagus. Their patient, a 53-year-old man, had a relatively benign presentation, and on the third hospital day a contrast swallow X-ray was performed, showing a subphrenic leak. At laparotomy an extraperitoneal abscess was found in relation to a left posterior oesophageal perforation. Simple drainage was carried out. A left subphrenic abscess developed and was drained. The oesophagocutaneous fistula which developed closed spontaneously. The patient had been shown to have a small sliding hiatus hernia and a scarred duodenal bulb more than a year earlier, and had previously also complained of mild dysphagia. The authors attributed the rupture to cardiospasm causing hold-up during swallowing, yet an oesophagocutaneous fistula would be unlikely to close spontaneously if it were proximal to an obstruction.

The case presented here was similar to that of Strauch and Lynch: both were subphrenic and extraperitoneal, but while their case was of benign presentation, without mediastinitis, the present case was very ill from the outset.

As to the aetiology of the present case, the rupture was caused by vomiting and some agency was necessary to occlude the oesophagus above the site of rupture. It is suggested that the oesophagus was occluded by the diaphragm, which contracted inappropriately but forcefully at the moment of emesis. The glottis closes during vomiting, and the diaphragm certainly becomes 'fixed' as a result. There was no other possible anvil upon which the advancing hammer of vomit could strike the oesophagus.

Discussion

Presentation

Most cases of Boerhaave's syndrome present within a few hours of perforation, although some cases present days later. Many, despite presenting early, are not diagnosed for some days. The impressive clinical feature is the sudden severe pain, not responding to powerful analgesics, and situated in the retrosternal and epigastric regions. It may also radiate to the hypochondria, the renal areas, the shoulders, or the middle of the back. The patient is usually profoundly ill, suggesting myocardial infarction, perforated peptic ulcer, pancreatitis or dissecting aortic aneurysm. The upper abdomen is usually tender and rigid. The most important diagnostic sign is surgical emphysema palpable at the sternal notch and, rarely, even extending up into the face (Russell and MacDonald, 1968). This sign, however, also occurs in lacerations or rupture of the trachea or main bronchi, and for this the treatment is quite different. While surgical emphysema is usually present early, especially in the higher perforations, several cases have been reported where this sign was long delayed or completely absent. It was found in only 7 of the 12 cases reported by Keighley and his colleagues (1972).

In most cases examination of the lung fields reveals the signs of an effusion or hydropneumothorax. Aspiration of the effusion may show an acid pH or frank gastric contents. Initially it may be sterile and serous, but bacteria nearly always appear later. The amylase concentration may be raised due to swallowed saliva in the effusion. The 'tetrad of Goth' attached to Boerhaave's syndrome comprises prostration, respiratory distress, chest pain and crepitus in the sternal notch. Hamman's sign, a 'mediastinal crunch' audible in the precordium, may be elicited.

Investigations

Investigations usually show normal haemoglobin concentration, a neutrophil leucocytosis, normal plasma urea and electrolytes and normal amylase, although Boerhaave's syndrome has been reported as a complication of pancreatitis. The cardiograph is normal in most cases.

Plain X-rays of the chest and abdomen may show an effusion, commonly on the left side, and mediastinal widening. Differentiation from thoracic aortic dissection or aneurysm leakage may be difficult, but the vertical lines of mediastinal emphysema will seal the diagnosis (excepting tracheal or bronchial perforation). Spontaneous pneumomediastinum and pneumopericardium have also been described in anorexia nervosa but the presentation is benign compared with oesophageal rupture (Donley and Kemple, 1978). In order to demonstrate emphysema, however, the X-rays have to be of good quality and adequate penetration, so that 'portable' X-rays of a restless, semi-recumbent patient are rarely helpful. Under ideal viewing conditions, later examination of the chest X-ray of the case reported here showed faint lines of mediastinal emphysema but these were not observed at the time of admission. Both posteroanterior and lateral views should be obtained. When the topic was reviewed by Toghill et al. in 1968, air had never been shown below the diaphragms, but this has now been reported by Bruno et al. (1963), Keighley et al. (1972) and Thornley and Wallwork (1978). Pneumopericardium was reported by Mansour and Teaford (1973) but the case they described had previously undergone oesophagogastrectomy for a benign stricture of the lower oesophagus and subsequent fundic patch oesophagoplasty for recurrent stricture, 14 months before final presentation with oesophageal rupture into the pericardium.

The V-sign of Naclerio is the outlining by extrapleural gas of the mediastinal and diaphragmatic pleurae (posteroanterior view).

To confirm the diagnosis and locate precisely the site of the rupture, a contrast swallow is undertaken. Gastrografin passes too quickly and leaked barium causes a severe tissue reaction; iodized oil (10–20 ml) is recommended (Triggiani and Belsey, 1977). The patient may be too ill to cooperate, however, and a small supradiaphragmatic collection may be mistaken for a paraoesophageal hiatus hernia. In 1946, Barrett stated that there was a place for oesophagoscopy, and although various authors have regarded it as unrewarding or dangerous, there is no doubt that the modern flexible fibreoptic instrument will diagnose and locate perforation more surely than any other measure short of surgical exploration.

Furthermore, precipitating or associated diseases such as oesophageal varices, duodenal ulcer or hiatus hernia will be detected and, more important, oesophageal lesions such as carcinoma, stricture or impacted foreign body or food will be obvious when they could otherwise remain undetected. In one case when there was no surgeon available who was sufficiently experienced to perform thoracotomy, the perforation seen on endoscopy was intubated endoscopically to drain the mediastinum and instil antibiotics. The patient developed an empyema and oesophagocutaneous fistula requiring exploration, but he survived (Harma et al., 1968). This case also had a mild chronic stricture *below* the perforation.

Treatment

With the exception of cervical oesophageal perforations, which may usually be treated conservatively (Triggiani and Belsey, 1977), once oesophageal rupture has been diagnosed, formal surgical exploration is mandatory. The survival rate varies inversely with the time elapsed from perforation to operation. While there have been reports of spontaneous recovery on conservative measures (Sanderson, 1965; Hammerschmidt et al., 1973), these are unusual rather than trend-setting.

There are differences between vomiting-induced and instrumental perforations of the oesophagus. The high pressure injection of septic vomit into the mediastinal tissue planes causes a severe reaction which is graphically described in the published literature on the subject. The description is of a blackened, bulging mediastinal pleura disgorging an offensive mixture of blood and vomit, with much devitalized tissue. An instrumental perforation is by comparison a relatively sterile and gentle process. The longer delay before diagnosis in Boerhaave's syndrome compounds the morbidity and mortality, especially when the patient uses this time to slake his thirst, as he often does. Thus, mortality is much greater, taken overall, in Boerhaave's syndrome than in instrumental perforation.

As soon as the diagnosis is suspected, broad spectrum antibiotic treatment should be commenced. Thoracotomy on the appropriate side provides adequate access in most cases, but in a low perforation extending below the diaphragm a left thoracoabdominal approach has advantages (Craddock, 1968). For subphrenic extraperitoneal perforations without extension of the rupture above the diaphragm, however, a purely abdominal approach cannot be recommended. In the case reported here the surgery performed was not excessively delayed and achieved a sound repair of the perforation. The antibacterial measures taken were both prompt and thorough. The bacteria isolated are presumed to have been the cause of the suppuration, but despite carefully monitored levels of appropriate antibiotics, sepsis was uncontrolled and appears to have been the cause of death. Blood cultures and culture of the central venous catheter tip were all sterile, as were the pleural effusions, which is most unusual.

Peritoneum and pleura cope well with, and contain, sepsis as a rule whereas mediastinitis is lethal. Gas permeates through the mediastinal tissues following oesophageal rupture and presumably bacteria accompany the gas. The extensive fasciotomy and drainage provided by the more usual transthoracic approach may be essential to the management of mediastinal cellulitis, and possibly more important than systemic antibiotic therapy. Thoracotomy is therefore indicated even in low ruptures.

It may be that oesophageal rupture with perforation into a pleural cavity carries a better prognosis than when the infective process is confined to the mediastinum, on purely pathological grounds. This would be difficult to prove, however, since the early appearance of a pleural effusion leads to earlier diagnosis and treatment than in the more occult cases.

The overall mortality remains high, but prompt treatment in specialized units produces excellent results. Triggiani and Belsey (1977) reported 1 death out of 11 cases over 25 years. Five of these cases were diagnosed 24 h or more after perforation, yet 4 survived. The survival of the late-presenting cases, however, demands drastic measures which may be outside the usual repertoire of the general surgeon. The primary, life-saving measure is not beyond him, however, and the secondary reconstruction may be contemplated at leisure.

The early case with little contamination should be débrided and then meticulously repaired in layers. The visible muscle split is usually shorter than the mucosal tear. Keighley and his colleagues showed that the muscle split was 2 cm shorter in the 7 cases in whom accurate measurements were taken (Keighley et al., 1972). Others have made the same observation. The muscle split must therefore be extended before the mucosa is sutured. Interrupted sutures are used, with catgut, silk and stainless-steel wire all having their advocates. Stainless-steel wire, however, causes the least reaction in already inflamed tissue.

If there is an extensive defect in the oesophagus following débridement, it is possible to use adjacent tissues to make good the defect. Thal and Hatafuku (1964) described the successful use of an intact fold of gastric fundus mobilized above the diaphragm and sutured to the edges of the defect. Millard (1971) used a pericardial flap to repair a defect resulting from necrosis of a previously repaired rupture.

Hatcher (1973) described his experience with the use of a T tube to intubate the oesophagus at the site of rupture, both traumatic and spontaneous. While this method necessarily establishes an oesophago-cutaneous fistula, this closes spontaneously in a high proportion of cases. Harrison et al. (1976) reported 5 survivors in 7 cases who presented late (average 57 h after perforation) using this method. A wide-bore tube is used.

Mayer et al. (1977) reported 5 cases of oesophageal perforation—3 spontaneous—with delayed recognition. Their experience underlines the need for prompt surgery and ruthless débridement of dubious tissue without primary regard for oesophageal continuity.

In the series of Triggiani and Belsey (1977), 2 patients were treated with pleural drainage and jejunostomy feeding only. One died of sepsis while the other developed a chronic empyema. Primary suture was carried out in 4, but in 5 resection was necessary. One case underwent oesophagogastrostomy, but 4 cases needed oesophagectomy with cervical oesophagostomy and gastrostomy. Colonic interposition at a later stage restored continuity.

Conclusion

As other authors have speculated, this condition is probably more common than is realized. Massive myocardial infarction, thoracic aortic dissection, overwhelming pneumonia, exsanguination from varices, duodenal ulcer or multiple gastric erosions and severe pancreatitis are just a few of the diagnoses which may be written on the death certificate of the patient who has been admitted profoundly ill and died rapidly. For the clinician to be aware of the condition is the first step towards refuting its evil reputation.

References

ATKINSON M., BOTTRILL M. B., EDWARDS A. T. et al. (1961) Mucosal tears at the oesophagogastric junction (the Mallory–Weiss syndrome). *Gut* **2**, 1–11.

BARRETT N. R. (1946) Spontaneous perforation of the oesophagus. *Thorax* **1**, 48–70.

BRUNO M. S., GRIER W R. N. and OBER W. B. (1963) Spontaneous laceration and rupture of esophagus and stomach. *Arch. Intern. Med.* **112**, 574–583.

CALLAGHAN J. (1972) Boerhaave syndrome. *Br. J. Surg.* **59**, 41–44.

CRADDOCK D. R., LOGAN A. and MAYELL M. (1968) Traumatic perforation of oesophagus and stomach. *Thorax* **23**, 657–662.

DONLEY A. J. and KEMPLE T. J. (1978) Spontaneous pneumomediastinum complicating anorexia nervosa. *Br. Med. J.* **2**, 1604–1605.

EDWARDS D. A. W. (1969) In: SHANKS S. C. and KERLEY P. (ed.) *A Textbook of X-ray Diagnosis*, 4th ed. London, Lewis, vol. 4, pp. 316–317.

HABEIN H. C. (1977) Ehlers–Danlos syndrome with spontaneous rupture of the esophagus: report of a first case. *Rocky Mt Med. J.* **74**, 78–80.

HAMMERSCHMIDT D., BADERTSCHER V. and SILVIS S. E. (1973) Spontaneous rupture of the oesophagus: report of a case with benign presentation and spontaneous resolution. *Am. J. Gastroenterol.* **60**, 165–170.

HARMA R. A., KOSKINEN Y. O. and SUURKARI S. O. (1968) Spontaneous rupture of the oesophagus: endoscopic treatment in the primary stage. *Thorax* **23**, 210–213.

HARRISON M. W., LINDELL T. D. and BRANT B. (1976) Surgical treatment of late esophageal perforation. *Am. Surg.* **42**, 488–491.

HATCHER C. R., HARDY J. D. et al. (1973) Contribution to discussion in: Esophageal perforations and fistulas. *Ann. Surg.* **177**, 788–797.

HOLMES K. D. (1966) Mallory–Weiss syndrome: review of 20 cases and literature review. *Ann. Surg.* **164**, 810–820.

HOLT S., MILLAR J. W., HEADING R. C. et al. (1978) Spontaneous mid-oesophageal rupture. *Postgrad. Med. J.* **54**, 559–565.

KEIGHLEY M. R. B., GIRDWOOD R. W., IONESCU M. I. et al. (1972) Spontaneous rupture of the oesophagus: avoidance of postoperative morbidity. *Br. J. Surg.* **59**, 649–652.

KELLEY D. L., NEUGEBAUER M. K. and FOSBURG R. G. (1972) Spontaneous intramural esophageal perforation. *J. Thorac. Cardiovasc. Surg.* **63**, 504–508.

MANSOUR K. A. and TEAFORD M. D. (1973) Atraumatic rupture of the oesophagus into the pericardium simulating acute myocardial infarction. *J. Thorac. Cardiovasc. Surg.* **65**, 458–461.

MAYER J. E., MURRAY C. A. and VARCO R. L. (1977) The treatment of esophageal perforation with delayed recognition and continuing sepsis. *Ann. Thorac. Surg.* **23**, 568–573.

MILLARD A. H. (1971) Spontaneous perforation of the oesophagus treated by the use of a pericardial flap. *Br. J. Surg.* **58**, 70–72.

MORI S., KASAI M., WATANABE T. et al. (1977) Spontaneous rupture of the esophagus. *Gastroenterologica Japonica* **12**, 70–79.

PENKA W. E., EDWARDS W. D., PRESKORN W. H. et al. (1977) The deadliest rupture: idiopathic muscular hypertrophy of the esophagus. *J. Kansas Med. Soc.* **78**, 269–275.

RUSSELL J. Y. W. and MACDONALD N. (1968) Spontaneous rupture of the oesophagus. *Br. J. Surg.* **55**, 311–314.

SANDERSON R. G. (1965) Spontaneous rupture of the esophagus: report of survival without surgical management. *Am. J. Surg.* **109**, 506–508.

SENCERT (1911) Perforation of the abdominal oesophagus. *Soc. Chir. Bull. Mem.* **37**, 1046–1051.

SMITH G., BRUNNEN P. L., GILLANDERS L. A. et al. (1974) Oesophageal apoplexy. *Lancet* **1**, 390–392.

STILWELL J. H. (1978) Intrathoracic perforation of hiatus hernia. *Br. Med. J.* **2**, 605–606.

STRAUCH G. O. and LYNCH R. E. (1965) Subphrenic extrathoracic rupture of the esophagus. *Ann. Surg.* **161**, 213–217.

THAL A. P. and HATAFUKU T. (1964) Improved operation for esophageal rupture. *JAMA* **188**, 826–828.

THORNLEY P. E. and WALLWORK J. (1978) Spontaneous rupture of the oesophagus and massive pneumoperitoneum. *Br. J. Surg.* **65**, 633.

TIDMAN M. K. and JOHN H. T. (1967) Spontaneous rupture of the oesophagus. *Br. J. Surg.* **54**, 286–292.

TOGHILL P. J., MACGUIRE C. F. and RAUT P. S. (1968) Spontaneous rupture of the healthy oesophagus. *Postgrad. Med. J.* **44**, 504–508.

TRIGGIANI E. and BELSEY R. (1977) Oesophageal trauma: incidence diagnosis and management. *Thorax* **32**, 241–249.

VAN DE VELDE J. M., CORMAN J. and PELOQUIN A. (1976) Boerhaave's syndrome: clinical observations. *Union. Med. Can.* **105**, 1544–1551.

WATTS H. D. (1976) Lesions brought on by vomiting. The effect of hiatus hernia on the site of injury. *Gastroenterol.* **71**, 683–688.

ZIKRIA B. A., ROSENTHAL A. D., POTTER R. T. et al. (1965) Mallory–Weiss syndrome and emetogenic rupture of the esophagus. *Ann. Surg.* **162**, 151–155.

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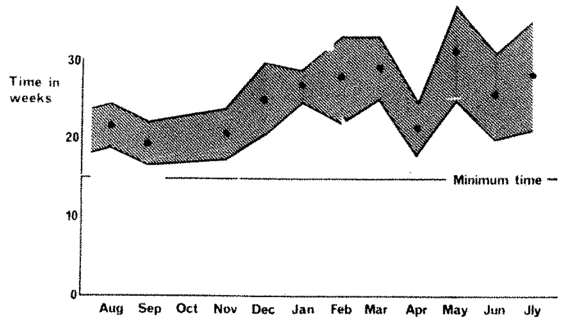

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Dysphagia following selective vagotomy

S. I. SULEIMAN, S. A. MAGLAD AND M. HOBSLEY*

SUMMARY

Progression of dysphagia after vagotomy to the stage of complete obstruction due to a peri-oesophageal fibrotic collar needing operation is a rare event. Review of the 4 such cases previously described, all needing further operation and all after truncal vagotomy, indicates that the oesophageal mucosa was normal on oesophagoscopy and that bouginage appeared to make the condition worse. This paper describes the first patient in whom (*a*) *the vagotomy was selective and* (*b*) *no bouginage was carried out before the condition was relieved by a further surgical operation.*

In this paper we describe a very rare cause of dysphagia following vagotomy and indicate how to diagnose and treat the condition.

Case report

A 58-year-old male Sudanese, with a 15-year history typical of duodenal ulcer pain, had recently started vomiting. The barium meal showed a deformed duodenal cap with pyloric outlet obstruction.

On 24 March 1976 he underwent selective vagotomy (Tanner, 1966) with a Heineke–Miculicz pyloroplasty. He made an uneventful recovery, started eating solid food on the fifth day and was allowed home on the tenth day on a full diet.

On 14 April the patient was readmitted complaining of dysphagia with a mild retrosternal pain and regurgitation. The dysphagia had commenced a week after discharge from hospital, i.e. 2 weeks after the operation. At first there had been difficulty only with solids, but within 3 days the dysphagia had progressed to complete inability to swallow.

Intravenous fluid therapy was started. When a barium swallow was performed the contrast medium reached the lower oesophagus and was regurgitated. Fibre-endoscope oesophagoscopy showed a normal mucosa but the lumen of the lower oesophagus was irregular and narrowed and would not yield to the 7-mm fibre endoscope. After 48 h a thin Gastrografin swallow showed a narrowed lower oesophagus and there was a trickle of contrast medium into the stomach (*Fig*. 1).

On 18 April the patient was re-explored. The lower oesophagus, denuded at the previous operation, was found to be surrounded by tough fibrous tissue, particularly anteriorly and laterally. The fibrous tissue was easily dissected from the oesophageal muscle but was firmly adherent to the peri-oesophageal tissue. The fibrotic collar was removed and both silk sutures previously used for ligating the vagal trunks were found amidst the tough tissues. The patient's postoperative recovery was uneventful and he could swallow solid food within a week. At follow-up, 18 months later, the patient remained symptom-free.

Discussion

Many believe that vagotomy denervates the lower oesophageal sphincter mechanism and leads to loss of peristalsis and a form of achalasia (Moses, 1947; Harris and Miller, 1960). However, Edwards (1970) showed by radiology and manometry in patients with post-vagotomy dysphagia that the lower oesophageal sphincter was intact and that peristalsis occurred normally. Denervation of the lower oesophagus in dogs is only achieved by vagal section high in the hila of the lungs (Carveth et al., 1962); this may be why the incidence of dysphagia is higher after transthoracic vagotomy (Grimson et al., 1947) than after abdominal vagotomy (Wirthlin and Malt 1972).

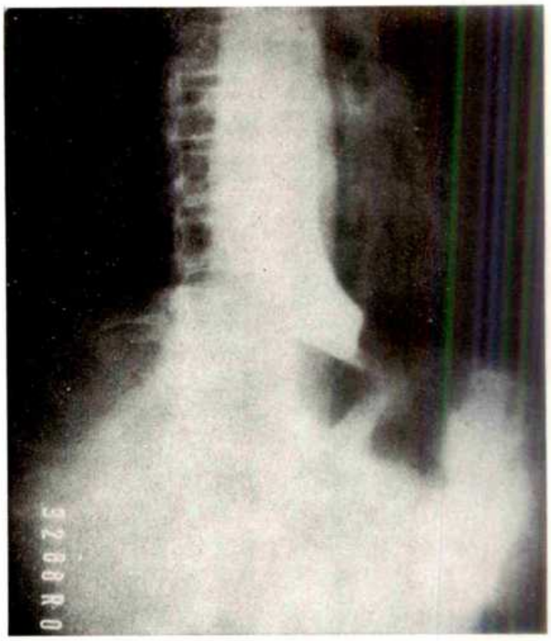

Fig. 1. Gastrografin swallow showing narrowing of the lower oesophagus which proved to be due to peri-oesophageal fibrosis.

Post-vagotomy dysphagia can certainly be caused by oesophagitis due to reflux, with or without a hiatus hernia (Beal, 1948; Clarke et al., 1965; Johnson, 1965). Reflux oesophagitis can be diagnosed by oesophagoscopy.

The literature (Bruce and Small, 1959; Guillory and Clagget, 1967; Postlethwaite et al., 1969; Spencer, 1975) also describes 4 patients after truncal vagotomy in whom operation was needed to relieve complete oesophageal obstruction due to pressure from a fibrous collar. In all cases the dysphagia started 2–3 weeks following the vagotomy, oesophagoscopy—when performed—showed a normal mucosa and dilatation of the oesophagus was ineffectual. It is particularly interesting to note the comment of Postlethwaite et al. (1969) that 'for 2 months repeated dilatations were performed but the size of the oesophageal lumen gradually decreased'.

Our patient is the first in whom this rare form of dysphagia occurred after selective vagotomy. Presumably the condition can also arise after proximal gastric vagotomy, as in all forms of vagotomy the lower oesophagus is denuded. The differentiation of

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this rare complication from dysphagia due to oesophagitis depends on the characteristically short time interval between the operation and the onset of symptoms (7–21 days), the relentless progression to complete, or nearly complete, inability to swallow and the finding on endoscopy of normal mucosa at the lower end of the oesophagus. The evidence of the previously described 4 cases suggests that bouginage is ineffective, because the rigid fibrotic collar cannot be stretched, and repeated attempts at bouginage cleary carry a risk of perforation of the oesophagus. We therefore suggest that the correct management should be early laparotomy and excision of the fibrous mass, without preliminary abortive attempts at oesophagoscopic dilatation. We successfully adopted this policy in the management of our patient.

References

BEAL J. M. (1948) Diaphragmatic hernia following subdiaphragmatic vagotomy. *Surgery* **24**, 625–627.

BRUCE J. and SMALL W. P. (1959) Dysphagia following vagotomy. *J. R. Coll. Surg. Edinb.* **4**, 170–178.

CARVETH S. W., SCHLEGEL J. F., CODE C. F. et al. (1962) Esophageal motility after vagotomy, phrenicotomy, myotomy and myomectomy in dogs. *Surg. Gynecol. Obstet.* **114**, 31–42.

CLARKE S. D., PENRE J. B. and WARD P. (1965) Oesophageal reflux after abdominal vagotomy. *Lancet* **2**, 824–826.

EDWARDS D. A. W. (1970) Post-vagotomy dysphagia. *Lancet* **2**, 90–92.

GRIMSON K. S., BAYLON G. J., TAYLOR H. M. et al. (1947) Transthoracic vagotomy. *JAMA* **134**, 925–932.

GUILLORY J. R. and CLAGGET O. T. (1967) Post-vagotomy dysphagia. *Surg. Clin. North Am.* **47**, 833–839.

HARRIS J. and MILLER C. M. (1960) Cardiospasm following vagotomy. *Surgery* **47**, 568–570.

JOHNSON J. R. (1965) Esophageal hiatus hernia following vagotomy. *Calif. Med.* **103**, 438–440.

MOSES W. R. (1947) Critique on vagotomy. *N. Engl. J. Med.* **237**, 603–610.

POSTLETHWAITE R. W., KIM S. K. and DILLON M. L. (1969) Esophageal complications of vagotomy. *Surg. Gynecol. Obstet.* **128**, 481–488.

SPENCER J. D. (1975) Post-vagotomy dysphagia. *Br. J. Surg.* **62**, 354–355.

TANNER N. C. (1966) A technique of selective vagotomy. *Br. J. Surg.* **53**, 185–189.

WIRTHLIN L. S. and MALT R. A. (1972) Accidents of vagotomy. *Surg. Gynecol. Obstet.* **135**, 913–916.

Paper accepted 13 March 1979.

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Anastomotic recurrence in the oesophagus complicating gastrectomy for adenocarcinoma of the stomach

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SUMMARY

Gastric adenocarcinomas often spread to the distal oesophagus. Failure to control the disease in this area during total and proximal subtotal gastrectomy results in recurrence at the oesophageal anastomosis. The incidence of recurrence in a series of 351 such patients was 10 per cent and was influenced by the location of the main lesion, the stage of the disease, the presence of tumour at the margin of resection and the length of clearance of the oesophageal margin. Recurrences were prevented only with in vivo *margins greater than 12 cm. Dysphagia combined with radiological signs of oesophageal obstruction was diagnostic of anastomotic recurrence regardless of the results obtained by oesophagoscopy and biopsy.*

Treatment was seldom effective in patients developing recurrence. Complete excision of the entire recurrent process offered the only hope for a long survival in these patients. Prevention by obtaining adequate oesophageal clearance at the time of gastrectomy is the only reasonable approach to this problem. The adequacy of resection cannot be judged accurately by intraoperative palpation of the oesophagus or by frozen section examination of the surgical margins.

OESOPHAGEAL invasion is common in patients undergoing proximal subtotal or total gastrectomy for primary gastric adenocarcinoma, the incidence depending on the location of the main lesion in relation to the gastro-oesophageal junction. Thus, 30–90 per cent of all resectable adenocarcinomas of the cardia (Pack, 1949; Morson, 1961; Paulino and Roselli, 1973) and 25 per cent of corpus primaries (Paulino and Roselli, 1973) invade the distal oesophagus either directly or by embolization of intramural and peri-oesophageal lymphatics (Morson, 1961). Failure to eradicate the entire invading process in the oesophagus of such patients may predispose to neoplastic recurrence at the oesophageal anastomosis following resection.

Theoretically, recurrence of a resected gastric neoplasm at the oesophageal anastomosis may be due to, first, neoplastic remnants left behind at the margin of resection following transection of the oesophagus through an area invaded by disease (Morson, 1961; Miller, 1962; Paulino and Roselli, 1973); incomplete resections of this type are reportedly encountered in 20–44 per cent of all gastric cancer patients undergoing total or proximal subtotal gastrectomy (Morson, 1961; Zinninger and Collins, 1965; Paulino and Roselli, 1973). The second cause may be skip submucosal lesions located above the line of oesophageal transection. These lesions are caused by intramural permeation of the disease (Morson, 1961) and can be easily missed intraoperatively. The third cause may be infiltration of the peri-oesophageal tissues in the posterior mediastinum; according to Payne and Bernatz (1976) disease in the mediastinum is more often responsible for these recurrences than failure to obtain tumour-free oesophageal margins.

Table I: INCIDENCE OF ANASTOMOTIC RECURRENCE IN THE OESOPHAGUS ACCORDING TO STAGE AND LOCATION OF THE GASTRIC TUMOUR

Location	Stage I and II	Stage III and IV	Total
Cardia	11/30 (36%)	14/54 (26%)	25/84 (28%)
Corpus	3/45 (6%)	7/148 (5%)	10/193 (5%)
Total	14/75 (18%)	21/202 (10%)	35/278 (12%)

Recurrence of a gastric neoplasm at the oesophageal anastomosis is a grave complication which reduces the survival rate (Boyd et al., 1958; Miller, 1962; Humphrey and Kerstens, 1976) and re-establishes dysphagia. The present report is the first on this subject and examines the incidence, predisposing factors, clinical features, management and consequences of oesophageal anastomotic recurrence in 35 gastric cancer patients treated with total and proximal subtotal gastrectomy.

Patients and methods

The study involves 351 patients with primary adenocarcinoma of the gastric cardia ($n = 100$) and corpus ($n = 260$) treated with total ($n = 260$) or proximal subtotal ($n = 91$) gastrectomy between 1950 and 1975 at Memorial Sloan-Kettering Cancer Center. Oesophagoscopic and upper gastrointestinal X-ray studies preceded all operative procedures. The adequacy of oesophageal resection during gastrectomy was determined by palpation of the oesophagus. Frozen section examination of the surgical margins was carried out in 130 patients. Resected neoplasms were classified according to the TNM system (American Joint Commission for Cancer Staging and End Results Reporting, 1971). Specimen dimensions were obtained from available pathology reports. The macroscopic margin of an oesophageal specimen was defined as the distance between the palpable periphery of the main lesion and the line of oesophageal transection. The microscopic margin was the distance between the microscopic border of the main lesion and the same line. These measurements were carried out in fresh specimens and they must be doubled in order to correspond to *in vivo* dimensions (Miller, 1962; Rosi, 1969). Patients developing anastomotic recurrence were readmitted to the same hospital where histological confirmation of the diagnosis was always obtained.

Results

Incidence

The overall incidence of anastomotic recurrence in the present series was 10 per cent (35/351); among patients who survived their operation and became liable to recurrence the incidence was 12 per cent (*Table I*). The incidence was markedly influenced by the location of the primary tumour and the TNM stage (*Table I*). Thus, recurrences appeared in 28 per cent of patients with neoplasms of the gastric cardia as compared with only 5 per cent of those who had primaries of the corpus ($P < 0.001$, χ^2 test). Patients

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Table II: INCIDENCE OF ANASTOMOTIC RECURRENCE IN THE OESOPHAGUS ACCORDING TO SIZE OF OESOPHAGEAL MARGINS

Macroscopic margin*	Survivors	Recurrence rate
0 cm	16	2 (12%)
1 mm–2 cm	61	10 (16%)
2·1 cm–4 cm	134	18 (13%)
4·1 cm–6 cm	50	5 (10%)
>6 cm	17	0 (0%)
Total	278	35/278 (12%)

* Specimen dimensions.

with early stage disease seemed more prone to anastomotic recurrence than patients with advanced stage disease regardless of tumour location (*Table I*). Thus, the incidence of recurrence was 18 per cent following treatment of TNM stage I and II disease as compared with 10 per cent following treatment of stage III and IV lesions, but the difference was not statistically significant ($P<0·1$).

Oesophageal margins

Transection of the oesophagus close to the tumour predisposed to recurrence at the oesophageal anastomosis. This was indicated by two facts: (*a*) the median length of the macroscopic oesophageal margins in patients who eventually developed recurrence was only 1·5 cm (range 0–6 cm) as compared with 2·9 cm (0–9 cm) in patients remaining free from anastomotic recurrence ($P<0·05$, rank sum test); (*b*) the incidence of anastomotic recurrence declined as the median length of the macroscopic oesophageal margins increased (*Table II*). Recurrences were not encountered among 17 patients whose oesophageal margins were 6 cm or more in length. The low incidence of recurrence among patients in whom the oesophagus was divided at the edge of the tumour (*Table II*) is explained by the fact that these patients were treated for palliation and only a few of them survived long enough to develop local recurrence.

In 20 per cent of the patients (73/381) the line of oesophageal transection was found to be invaded by tumour, i.e. the length of the microscopic margin was zero. The incidence of recurrence in these patients was 16 per cent (12/73); it increased, however, to 23 per cent when calculations included only patients who survived their operations (12/53). The same incidence in patients with histologically free oesophageal margins was 10 per cent (23/227). The difference was statistically significant ($P<0·001$, χ^2 test). Thus, histologically positive oesophageal margins were responsible for only 34 per cent of all anastomotic recurrences (12/35), the remainder being caused by other factors. Histologically positive margins were not contributory to the high incidence of anastomotic recurrence observed in patients with tumours of the gastric cardia because they were only encountered in 36 per cent of them as compared with 40 per cent of patients operated upon for tumours arising in the corpus of the stomach.

Extent of oesophageal invasion

Recurrences were mainly associated with neoplasms arising high in the stomach and involving segments of oesophagus. The median length of oesophagus macroscopically occupied by tumour was only 0·8 cm (range 0–2·2 cm) in patients who remained free from recurrence as compared with 2·3 cm (range 1·5–5 cm) in those who developed anastomotic recurrence ($P<0·05$, rank sum test). Microscopic spread of the neoplasm beyond its palpable edge was present in most of the specimens and was either continuous with the primary or discontinuous, forming skip submucosal foci proximal to it. Invasion in continuity with the main neoplasm was confined within a maximum radius of 4 cm from its macroscopic border, while discontinuous spread was confined within a 6 cm radius. Two patients were exceptional in this regard because they had involvement of the entire oesophagus extending all the way to the thoracic outlet. Both these patients died following re-exploration undertaken for the eradication of all disease from the oesophagus.

Frozen section examination of the oesophageal margin before construction of the anastomosis was carried out in 130 patients. Ten of them subsequently developed recurrence at the anastomosis despite the fact that their margins were clear histologically (7·6 per cent incidence). The incidence of anastomotic recurrence among patients operated upon without the use of frozen section examination was 11 per cent (25/221). The difference between the two groups was not statistically significant.

Clinical manifestations

Dysphagia was present in all patients who had recurrence at the anastomosis. Dysphagia was persistent and progressive. Patients postponed medical consultations for an average of 38 days, attributing their symptoms to a variety of 'benign' causes such as 'ulcer', 'dyspepsia' etc. Additional delay in treatment was occasionally caused by the physicians, who insisted on obtaining histological proof of recurrence before initiating therapy. Thus, 5 patients were subjected to multiple oesophagoscopic examinations because oesophageal biopsies were negative. When finally diagnosis was confirmed histologically, none of these patients was in a position to undergo effective treatment. False negative oesophageal biopsies were common in the present series and were caused by sampling of normal oesophageal mucosa overlying the recurrent process.

Recurrences were best diagnosed by a barium swallow examination (*Fig.* 1). Radiological signs of oesophageal obstruction at the site of the anastomosis combined with a history of persistent dysphagia were virtually diagnostic of anastomotic recurrence. This combination was present in all 35 patients. There was only one patient in the entire series who presented with such a combination and yet he was found to have oesophageal obstruction caused by a band of adhesions. Dysphagia was relieved following re-exploration and division of the constricting band in this patient.

Management

Patients developing anastomotic recurrence were best treated with re-exploration and resection of the recurrent process. Resections were effective only when they did not leave tumour in the mediastinum and oesophagus. This was accomplished in only 4 patients out of 12 re-explored. Two of the 4 are still alive 2½ and 3½ years later; the remaining 2 died postoperatively from surgical complications. Incomplete resections were carried out in 4 patients all of whom died within 3 months from second recurrence in the chest and/or generalized metastases. Nine patients were managed with radiation therapy; 5 succumbed during treatment and 4 experienced transient palliation. None of them lived more than 5 months. Oesophageal dilatations were carried out in 3 patients who subsequently received radiation therapy and 2 other patients were managed with intubation of the oesophagus. The longest survivor in this group was a patient whose oesophageal tube continued to function for 6 months until he died from distant metastases. All other patients succumbed within 4 months. Finally, 3 patients were managed with a feeding gastrostomy; 1 survived the procedure with palliation for 3 months, the other 2 died from surgical complications or from aspiration.

Prognosis

Anastomotic recurrence had a profound impact: the median survival after the onset of dysphagia was only 5 months and only 2 out of 35 patients developing recurrence lived beyond the third postoperative year. These two individuals were the only long term survivors out of 14 patients with stage I and II lesions who developed recurrence. These results should be compared with a 55 per cent 5-year actuarial survival of stage I and II patients who did not develop anastomotic recurrence. The difference in survival between stage III and IV patients with and without recurrence was less striking. Thus, there were no 2-year survivors among stage III and IV patients developing recurrence at the anastomosis, while the 2-year actuarial survival of their counterparts who did not develop recurrence was 21 per cent. Most importantly, those who did not develop recurrence died under much better circumstances than patients with recurrence.

Discussion

Recurrence of a gastric neoplasm at the oesophageal anastomosis is due to inadequate local control of the disease in the oesophagus and the posterior mediastinum (Payne and Bernatz, 1976) and appears to be a common late postoperative complication of total and proximal subtotal gastrectomy (Miller, 1962). Its incidence mainly depends on the location of the primary neoplasm in relation to the oesophagus (Miller, 1962), the adequacy of oesophageal resection (Miller, 1962; Humphrey and Kerstens, 1976; Payne and Bernatz, 1976) and, as this study showed, on the stage of the disease at the time of surgery. Its real incidence must be higher than that reported because it is unknown how many patients who die from metastases have oesophageal recurrence but not dysphagia. Indeed, autopsies performed in patients dying 6–37 months after proximal subtotal gastrectomy for adenocarcinoma of the cardia revealed recurrence at the anastomosis in 55 per cent according to one report (Humphrey and Kerstens, 1976).

Of all gastric neoplasms in this series, those arising in the cardia were the most prone to anastomotic recurrence (*Table I*). Miller (1962) reported a similar incidence in his series. Adenocarcinomas of the cardia reportedly demonstrate the same ability to cause widespread intramural invasion of the oesophagus as squamous oesophageal primary carcinomas (Humphrey and Kerstens, 1976) and they are far more dangerous in this regard than lesions arising in the gastric corpus (Paulino and Roselli, 1973). In a histological study conducted in patients with resectable adenocarcinomas of the cardia Morson (1961) detected invasion of the oesophagus in 90 per cent of the specimens; in 60 per cent of the specimens there was microscopic spread of the disease beyond a 2·5-cm radius from the palpable edge of the main lesion. The high incidence of recurrence among patients with lesions of the cardia in our study could not be attributed to the adequacy of resection because histologically positive oesophageal margins were present in 36 per cent as compared with 40 per cent of patients with corpus tumours. One may speculate here that neoplasms of the cardia tend to cause skip intramural metastases and invasion of the peri-oesophageal tissues in the way that primary oesophageal neoplasms do, hence they ought to be treated with wider margins than corpus lesions.

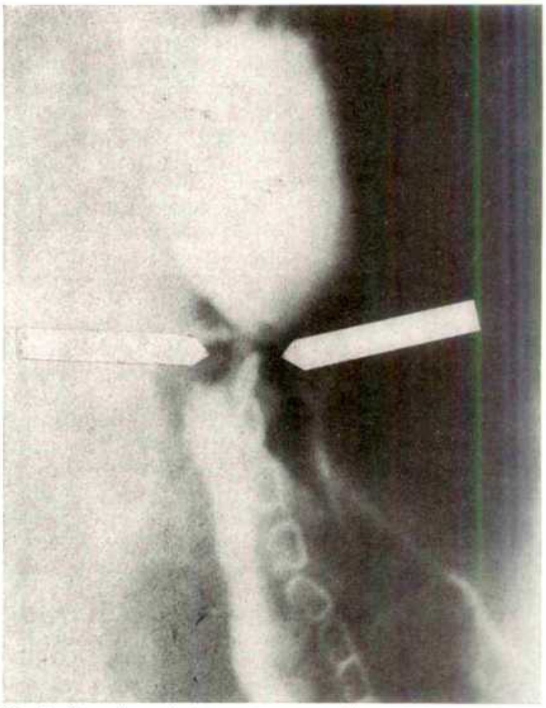

Fig. 1. Oesophageal obstruction caused by recurrence of a gastric neoplasm at the anastomosis following proximal subtotal gastrectomy.

Recurrences were more common in patients with early rather than advanced stage lesions. Patients with early stage disease live longer and have a greater chance of developing recurrence at the anastomosis, while stage III and IV patients usually succumb early due to distant metastases before the appearance of anastomotic recurrence. For the same reason the effect of recurrence on survival was far greater among patients with early rather than advanced stage disease. Studies conducted in our institution showed that surgical treatment makes a difference in patients with TNM stage I and II lesions only, while stage III and IV patients are seldom benefited by it (Papachristou and Fortner, 1979). Considering these facts and the poor prognosis of patients developing recurrence, prevention of this complication by adequate surgery is of enormous importance in patients with early stage disease.

The question as to what constitutes an adequate oesophageal resection in the treatment of gastric neoplasms is difficult to answer. Surgeons have traditionally used palpation and frozen section examination of the oesophageal margin to determine the adequacy of resection (Pack, 1949). It appears that both these methods can be inaccurate for two main reasons. First, the macroscopic boundaries of the neoplasm in the oesophagus rarely coincide with the microscopic ones, hence palpation can mislead the surgeon. Thus, the recurrence rate was not reduced significantly in our series when margins of 2–3 cm in length were obtained. These margins correspond to 4–6 cm *in vivo* (Miller, 1962). Even with macroscopic margins as long as 4–6 cm, i.e. 8–12 cm *in vivo*, recurrences were not prevented. Some of the patients with 4–6 cm margins had histologically positive margins despite the high levels of oesophageal transection. Secondly, the use of frozen section examination did not decrease significantly the incidence of anastomotic recurrence. Frozen section informs the surgeon whether or not tumour is present at the line of oesophageal transection. Frozen section does not detect skip submucosal lesions located above this level (Morson, 1961) or invasion of the peri-oesophageal tissues. All these facts suggest that palpation of the oesophagus above the tumour or frozen section of the oesophageal margin cannot determine accurately the adequacy of resection. What constitutes then an adequate margin?

The problem with comparing the various reports in regard to the size of oesophageal margins is that only a few take into consideration the fact that the oesophagus (Miller, 1962) and the rectum (Rosi, 1969) shrink to half their original size after resection and that it is almost impossible to reconstruct *in vivo* dimensions postoperatively (Payne and Bernatz, 1976). Thus, Humphrey and Kerstens (1976) believe that a 7-cm margin is the minimum requirement, while Payne and Bernatz (1976) consider a 4-cm margin as adequate. Both groups, however, recommend transection of the oesophagus at the level of the azygos vein if the tumour involves the cardia. Others (Garlock and Klein, 1954) recommend a supra-aortic anastomosis in such patients because transection of the oesophagus 3–6 cm above the lesion results in a high recurrence rate (Humphrey and Kerstens, 1976) despite the fact that a 6-cm margin usually includes all intramural disease (Miller, 1962). Recurrences in our series were prevented only with margins longer than 6 cm, which correspond to 12 cm *in vivo*. Margins of this size should probably be considered in the treatment of patients with early stage tumours and in those with primary neoplasms of the cardia since these are the patients who are particularly prone to anastomotic recurrence.

Patients developing anastomotic recurrence were rarely responsive to treatment. The only patients to benefit from it were those undergoing complete resection of the entire recurring process. Incomplete resections leaving tumour in the mediastinum were of no value. When resections were attempted in the face of advanced intrathoracic disease the mortality was high. Thus, resections should only be carried out if the tumour can be resected thoroughly with proper margins and no residual disease. Radiation therapy provided some palliation by alleviating dysphagia for a few months, although it failed to prolong the survival rate any more than other palliative methods such as oesophageal intubation or dilatation. For this reason radiotherapy ought to be reserved for those who cannot tolerate re-exploration and those with unresectable lesions.

References

AMERICAN JOINT COMMISSION FOR CANCER STAGING AND END RESULTS REPORTING (1971) pp. 1–9.

BOYD D. P., ADAMS H. D. and SALTZMAN F. A. (1958) Carcinoma of the esophagus. *N. Engl. J. Med.* **258**, 271–275.

GARLOCK J. H. and KLEIN S. H. (1954) The surgical treatment of carcinoma of the esophagus and cardia; an analysis of 457 cases. *Ann. Surg.* **139**, 19–28.

HUMPHREY E. D. and KERSTENS T. E. (1976) Adenocarcinoma of the gastroesophageal junction. In: VARCO R. L. and DELANEY J. P. (ed.) *Controversy in Surgery*. Philadelphia, Saunders, pp. 603–608.

MILLER C. (1962) Carcinoma of the thoracic oesophagus and cardia. *Br. J. Surg.* **49**, 507–522.

MORSON B. C. (1961) The spread of carcinoma of the esophagus. In: TANNER N. C. and SMITHERS D. W. (ed.) *Tumours of the Oesophagus*. Edinburgh, Livingstone, pp. 136–146.

PACK G. (1949) *Cancer of the Esophagus and Cardia*. St Louis, Mosby, pp. 145–188.

PAPACHRISTOU D. N. and FORTNER J. G. (1979) The choice of gastrectomy in patients with adenocarcinoma of the gastric cardia. *Ann. Surg.* (In the press).

PAULINO R. and ROSELLI A. (1973) Carcinoma of the stomach with special reference to total gastrectomy. *Curr. Probl. Surg.* December, pp. 13–32.

PAYNE W. S. and BERNATZ P. E. (1976) One-stage resection and reconstruction for carcinoma of the esophagogastric junction. In: VARCO R. L. and DELANEY J. P. (ed.) *Controversy in Surgery*. Philadelphia, Saunders, pp. 597–602.

ROSI P. A. (1969) Selection of operation for carcinoma of the colon. In: TURELL R. (ed.) *Diseases of the Colon and Rectum*. Philadelphia, Saunders, pp. 478–501.

ZINNINGER M. N. and COLLINS W. T. (1965) Extension of carcinoma of the stomach into duodenum and esophagus. *Ann. Surg.* **130**, 557–560.

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Bilio-pancreatic bypass for obesity: I. An experimental study in dogs

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SUMMARY

Bilio-pancreatic bypass is a new procedure that tries to obtain a maldigestion syndrome with selective malabsorption of the main high calorie foods. The operation consists of a gastric resection and division of the proximal jejunum just distal to the ligament of Treitz. A gastroentero-anastomosis is then constructed using the distal end of the transected jejunum, while the proximal jejunum is anastomosed to the side of the distal ileum.

An experimental study carried out on 12 dogs confirmed that the operation causes a selective malabsorption with loss of weight and no complications. On the basis of this study it is suggested that this procedure has the following advantages over jejuno-ileal bypass: (a) *normal absorption of bile salts, water and electrolytes;* (b) *slow recovery of absorption;* (c) *absence of a blind loop.*

JEJUNO-ILEAL bypass has become an established procedure for the surgical treatment of extreme obesity. Weight loss is satisfactory, but the operation is often followed by serious and sometimes fatal complications, such as intractable diarrhoea, electrolyte imbalance, hypovitaminosis, protein malnutrition, anorexia, nausea, vomiting, hepatic insufficiency, cholelithiasis, nephrolithiasis and polyarthritis. Some of these complications may be related to interruption of the enterohepatic bile salt circulation by the jejuno-ileal bypass; this interruption leads to the depletion of the bile salt pool, which favours the formation of gallstones (Wise and Stein, 1975; Scopinaro, Roda et al., 1976). Unabsorbed bile acids in the large bowel increase motility (Galapeaux et al., 1938; Meyer and McEwen, 1948), inhibit absorption (Mekhjian et al., 1968; Mekhjian and Phillips, 1970) and induce secretion of water and electrolytes (Mekhjian et al., 1971) causing diarrhoea and electrolyte imbalance.

The pathogenesis of nephrolithiasis after jejuno-ileal bypass is still controversial (Dickstein and Frame, 1973; O'Leary et al., 1974), but possible causes are the reduction of urine volume secondary to dehydration and hyperoxaluria due to excessive glycoxalate production from unabsorbed glycoconjugated bile salts in the colon (Wise and Stein, 1975). Moreover, the hepatic injury following intestinal shunt for obesity has been attributed to the hepatotoxic action of lithocholic acid (Drenick et al., 1970) and chenodeoxycholic acid (Sherr et al., 1974).

Malabsorption induced by jejuno-ileal bypass is extreme in the first months after operation, but the compensatory mechanisms quickly lead to the recovery of absorptive function (Scopinaro, 1974; Barry et al., 1977). As a result, a satisfactory final weight reduction necessitates exclusion of greater lengths of bowel, with an increased risk of complications (Jewell et al., 1975). Complications due to the blind loop include intussusception (Wise et al., 1976) and gastric hypersecretion (Buchwald et al., 1974; Danö and Van Nielsen, 1974; Scopinaro, Marugo et al., 1976; Solhaug and Schrumpf, 1976). The observations that hepatic injury does not occur after extensive small bowel resection (Kinney et al., 1962; Meyer, 1962; Bondat and Pisesky, 1967) and that it can be prevented after jejuno-ileal bypass by jejunostomy feedings (McClelland et al., 1970) suggest that a substantial role in the pathogenesis of liver damage must be attributed to the presence of a long intestinal loop excluded from the alimentary stream (Hollenbeck et al., 1975).

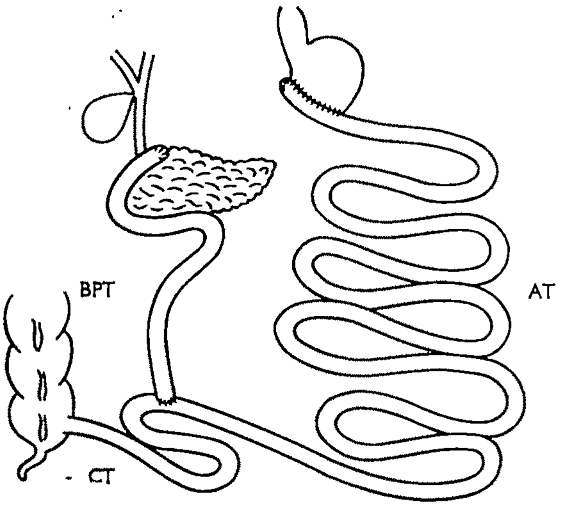

Fig. 1. Schematic representation of the operation of bilio-pancreatic bypass. BPT, Biliopancreatic tract; CT, common tract; AT, alimentary tract.

Bilio-pancreatic bypass is a new surgical procedure in which partial gastrectomy is performed, with closure of the duodenal stump. Gastrointestinal continuity is restored by a Roux-en-Y gastrojejunostomy, with the proximal end of the jejunum anastomosed to the distal ileum (*Fig.* 1). Three separate parts of the intestinal tract can then be recognized: the alimentary tract from the gastrojejunostomy to the jejuno-ileostomy; the bilio-pancreatic tract from the duodenal stump to the jejuno-ileostomy; and the common tract from the jejuno-ileostomy to the ileocaecal valve.

In the new anatomic situation the bilio-pancreatic secretion following meal intake reaches the distal ileum earlier than the undigested aliments which have to pass through a much longer intestinal tract. Provided that the ileal common tract is long enough to allow a normal absorption of bile salts, it is then

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possible to obtain a fat and starch maldigestion leaving the enterohepatic bile salt circulation undisturbed.

Since the alimentary transit through nearly the entire small bowel is preserved, jejuno-ileal absorption of water, electrolytes and hydrosoluble vitamins is allowed, while negative effects and complications due to the presence of the excluded bowel are avoided.

The degree of malabsorption depends on the digestive capacity of jejuno-ileal enzymes, on the residual or postprandial bilio-pancreatic secretion which is present in the distal ileum when the aliments reach the anastomosis, on the length of the common tract and on the transit time. Each of these factors may vary after operation, but the essential maldigestion system, based on the difference between bilio-pancreatic and alimentary transit time, is very unkely to be influenced by compensatory mechanisms.

Bilio-pancreatic bypass should then have the following advantages: (*a*) a selective instead of indiscriminate malabsorption; (*b*) a slow rather than rapid recovery of absorptive function; (*c*) the absence of the long loop of excluded bowel. In order to test the hypothesis that these advantages, if present, avoid the complications of jejuno-ileal bypass, a series of experiments was performed in the dog. This animal was chosen because it has been shown that the operation of jejuno-ileal bypass is followed by the same complications in the dog as in man (Kremen et al., 1954; Bondar and Pisesky, 1967; McClelland et al., 1970; Salmon, 1971; Hollenbeck et al., 1975).

Materials and methods

Twelve mongrel dogs weighing between 15 and 20 kg were fed a daily ration of a commercial dog food adequate to keep a stable body weight. The ration was divided into two equal meals and given to the dogs for at least 15 days before operation.

After the abdomen had been opened and the viscera inspected, the length of the small intestine was measured along its mesenteric border from the ileocaecal valve to the ligament of Treitz. A three-quarters distal gastrectomy was then performed, the duodenal stump being closed and the jejunum divided 20 cm distal to the ligament of Treitz. An anticolic antiperistaltic gastroentero-anastomosis was made using the distal end of the transected jejunum. The proximal end of the jejunum was finally joined end to side to the ileum. The distance of the anastomosis from the ileocaecal valve was equivalent respectively to: one-third of the intestinal length (70 cm approximately, group I, 3 dogs); one-sixth of the intestinal length (35 cm approximately, group II, 4 dogs); one-twelfth of the intestinal length (20 cm approximately, group III, 3 dogs). In 2 dogs (group IV, control group) only a three-quarters gastric resection and Billroth II gastrojejunostomy was performed. Before closing the abdomen a liver biopsy and a bile sample were obtained.

Pre- and postoperative investigations included blood count, blood sugar, blood urea nitrogen, serum total protein, albumin, bilirubin and alkaline phosphatase, SGOT and SGPT, electrolytes (Na, K, Cl, Ca, Mg and P), determination of the prothrombin time and complete urine examination.

Intestinal absorption of fat was evaluated by determination of the daily faecal fat excretion (mean of three consecutive days); protein absorption was determined by the radioactivity in faeces during the 48 h following administration of ^{125}I-albumin (5 mCi) with meals. To estimate intestinal absorption of bile salts, 5 mCi of 1-(^{14}C)-glycine-glycocholate were added to a daily ration of food and the ^{14}C faecal excretion during the subsequent 48 h was determined.

After operation the dogs were recommenced on their standard diet with the exception of the 3 dogs in group III who received food *ad libitum*. During this period all the animals were weighed weekly and studied carefully to ascertain the number and consistency of stools. After the first month the daily food ration of dogs in groups I and II was increased progressively until no further weight loss occurred. In order to compare pre- and postoperative absorption studies, supplementary meals were given without varying the amount of food at each meal. During this second follow-up period group I, II and IV animals were weighed monthly and group III animals weekly. After 1 year all the long term survivor dogs (groups I, II and IV) were sacrificed under anaesthesia. Post-mortem examinations were performed in all dogs.

Results

During the entire course of the experiment the dogs in group I had one daily formed bowel movement. They lost a mean of 20 per cent of their original weight during the first month and stopped losing weight when fed with about 150 per cent of the preoperative diet. Group II dogs had 2–5 daily soft stools in the first week after operation. Subsequently they showed a decrease in the number of stools and those passed became firmer in consistency. After 2 months they did not differ from the group I animals, except that the stool weight was greater. The dogs in this group lost a mean of 35 per cent of their initial weight during the first month and their weight stabilized when their intake was 250 per cent of the preoperative daily food ration. Dogs in group I and group II continued to keep a stable weight on their standardized increased diet. Group III dogs exhibited after the operation a severe and persistent diarrhoea, with up to 15 liquid bowel movements per day. They appeared to eat and drink more than before surgery but, despite this, continuously lost weight with the onset of dehydration and malnutrition. All the animals died during the second postoperative month, having lost more than 50 per cent of their original weight. When appearing close to death they were sacrificed under anaesthesia.

Dogs in group IV (control group) had no variations in frequency, consistency or weight of bowel movements following the operation. They showed an average of 10 per cent weight loss immediately after operation, followed by a progressive weight gain that stabilized by the fourth month at around preoperative levels.

Absorption studies

Preoperative determinations of fat and protein absorption were normal (less than 5 per cent faecal excretion) in all dogs. Absorption tests were repeated in groups I, II and IV at 1, 6 and 12 months after the operation. No absorption studies were performed in group III dogs as watery diarrhoea made it impossible to collect stools. In group I dogs 24·2 ± 7·9 per cent (mean ± s.d.) of fat intake was excreted in the faeces, and this decreased to 21·2 ± 3·9 at 6 months and 18·6 ± 3·7 at 12 months (*Fig*. 2).

In group II dogs the fat excretion was nearly double (one month, 43·3 ± 12·1 per cent; 6 months, 35·0 ± 6·9 per cent; 12 months, 32·2 ± 7·2 per cent) (*Fig*. 3). In the control group the pre- and postoperative studies were similar. The average ^{125}I-albumin faecal excretion in groups I and II showed a similar trend, with the greater loss in group II dogs (*Figs*. 2 and 3).

Bile studies

Bile salt metabolism was explored by evaluating pre- and postoperative intestinal absorption and gallbladder bile composition. Bile acid intestinal absorption was determined in groups I, II and IV before operation and 1, 6 and 12 months after surgery. Faecal excretion was within normal limits (less than 5 per cent of administered dose) in all instances before and after operation.

Gallbladder bile specimens were obtained by direct puncture at operation and at sacrifice in all dogs. Additional gallbladder punctures were performed 1 month and 6 months after operation in 1 dog from group I and in 2 dogs from group II after surgical exposure under anaesthesia. No significant alterations in bile composition were found after operation in groups I, II and IV. Bile analysis in group III animals demonstrated a marked postoperative fall in bile salt concentration (preoperative, 35·4 ± 4·3 mmol/l; postoperative, 24·2 ± 8·1 mmol/100 ml).

Electrolyte studies

Serum electrolyte determinations, performed weekly during the first month and subsequently at 3, 6, 9 and 12 months after operation, showed no postoperative changes in groups I, II and IV, with the exception of a slight transient decrease of potassium and calcium serum levels in the animals in group II at 1 to 3 weeks postoperatively. Dogs in group III exhibited a progressive fall in serum electrolyte concentration. Major deficiencies were observed for potassium, calcium and magnesium.

Liver studies

Wedge biopsies of the liver were taken from all dogs at operation and at sacrifice; in 1 dog from group I and in 2 dogs from group II wedge biopsies were performed under anaesthesia at 1 month and 6 months postoperatively. The liver biopsies showed no morphological abnormality. Liver function, as determined by measurement of serum bilirubin and alkaline phosphatase, SGOT and SGPT and prothrombin time, was unaltered at 1, 6 and 12 months in groups I, II and IV. Liver function tests were within normal limits in group III dogs at the time of sacrifice, despite the state of cachexia due to malnutrition.

Other biochemical findings

Studies on blood cells, serum protein, blood sugar, blood urea nitrogen and urine examination, performed postoperatively at the same time intervals as the electrolyte studies, demonstrated no alteration in dogs in groups I, II and IV. However, group III animals developed a progressive anaemia, hypoproteinaemia, increased blood urea level and ketonuria.

Other observations

An endoscopic examination of the gastrojejunostomy with pH determinations was done under anaesthesia 6 months after operation in 1 dog from group I and in 1 dog from group II. The mucosa of the gastric stump, the stoma and the proximal tract of the jejunal loop appeared normal in both instances. The secretion was minimal and the pH ranged between 5 and 7.

Intestinal length measurements were performed in 3 dogs at 6 months and in all the long term survivors at sacrifice. Changes were observed only in animals in groups I and II, with no significant difference between the two groups. The mean length of the alimentary tract increased by 21 ± 5 per cent 6 months after operation and by 35 ± 12 per cent at 12 months (mean ± s.d.). The mean length of the common tract was increased by 47 ± 15 per cent at 6 months and by 58 ± 17 per cent at 12 months. Histological examination showed mucosal hypertrophy, which was more pronounced in the common tract. Neither elongation nor microscopical change was demonstrable in the bilio-pancreatic tract.

At post-mortem examination, no macroscopic abnormality was noted. Histological examination of selected organs, other than the intestine, was normal.

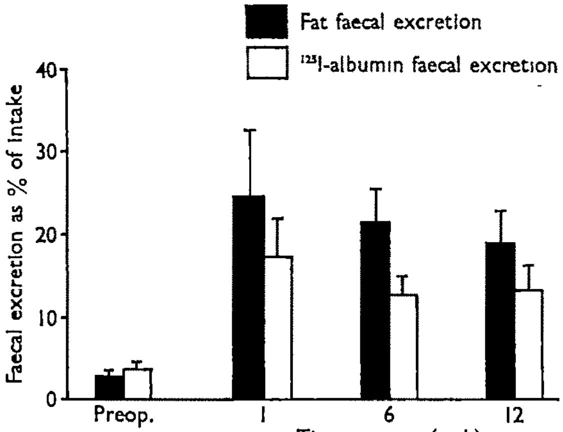

Fig. 2. Fat and protein malabsorption in dogs with one-third bilio-pancreatic bypass (group I).

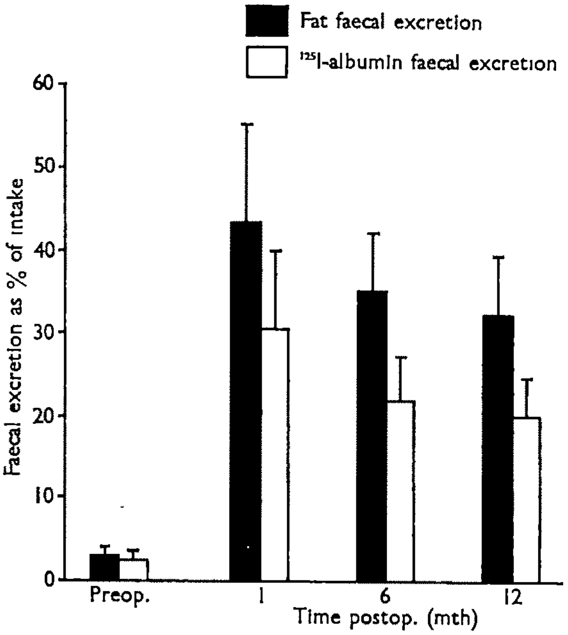

Fig. 3. Fat and protein malabsorption in dogs with one-sixth bilio-pancreatic bypass (group II).

Discussion

The main requirement of bilio-pancreatic bypass is that the ileal common tract is long enough to allow normal bile salt absorption. Three different experimental models were designed to assess the minimal length of this tract which would still prove adequate. Dogs in group III exhibited watery diarrhoea with altered bile acid metabolism, suggesting that a loop of distal ileum equivalent to one-twelfth of the total length of the small bowel is not sufficient for normal bile salt absorption. The experimental study was designed to demonstrate that bilio-pancreatic bypass causes selective malabsorption and to verify the absence of the complications and side effects which usually follow jejuno-ileal bypass.

The selective nature of the malabsorption due to the bilio-pancreatic bypass is shown in dogs in groups I and II by the absence of postoperative abnormalities, i.e. the number and consistency of stools, the serum electrolyte levels, the faecal excretion of bile salts and the gallbladder bile composition were all normal, while fat and protein intestinal absorption were reduced.

After jejuno-ileal bypass there is a tendency towards recovery of absorptive capacity after the first 6 months. The slow recovery of intestinal absorptive capacity after bilio-pancreatic bypass is suggested by the observation that animals in groups I and II, once they had lost weight, did not regain any significant weight even though they were kept for more than 10 months on the same diet. Despite malabsorption, no dog in group I or II exhibited postoperative diarrhoea or changes in serum electrolytes. Urinary or biliary calculi were never found at sacrifice. All the animals in groups I and II appeared active and in good health. Group III dogs appeared to have a serious bile salt malabsorption yet they had no functional or morphological signs of liver injury. This contradicts the theory that altered bile acid metabolism is an important factor in the pathogenesis of liver changes following jejuno-ileal bypass. On the contrary, our observations support the hypothesis that liver injury is due to the presence of a long intestinal loop excluded from the intestinal stream.

Bilio-pancreatic bypass is similar to the Mann–Williamson operation (Mann and Williamson, 1923) for the experimental production of peptic ulcer. The effect of gastrectomy with and without vagotomy on the course of the Mann–Williamson dog was investigated by Oliver (1949, 1951), who found that none of 6 animals with vagus section plus gastrectomy developed ulcers, while all 4 dogs with subtotal gastrectomy alone did develop ulcers. In contrast, Storer et al. (1950) showed that simple antrectomy was effective in preventing ulcer formation in 4 of 6 dogs with the Mann–Williamson operation. In our experimental series a three-quarters distal gastric resection has proved to be a sufficient measure to avert the risk of jejuno-ileal peptic ulceration during the 12-month follow-up.

From the results of this experimental study it is suggested that the operation of bilio-pancreatic bypass with insertion of the bypass into the ileum at a distance from the ileocaecal valve equivalent to one-sixth of the intestinal length allows adequate weight loss with minimal complications. It is recommended that this procedure overcomes many of the problems associated with the operation of jejuno-ileal bypass in the treatment of obesity.

References

BARRY R. E., BARISCH J., BRAY G. A. et al. (1977) Intestinal adaptation after jejunoileal bypass in man. *Am. J. Clin. Surg.* **30**, 32–42.

BONDAR G. F. and PISESKY W. (1967) Complications of small intestinal short-circuiting for obesity. *Arch. Surg.* **94**, 707–716.

BUCHWALD H., COYLE J. J. and VARCO R. L. (1974) Effect of small bowel bypass on gastric secretory function: post-intestinal exclusion hypersecretion, a phenomenon in search of a syndrome. *Surgery* **75**, 821–828.

DANO P. and VAN NIELSEN O. (1974) Effect of three types of intestinal shunt operation on gastric secretion in obesity. *Scand. J. Gastroenterol.* **9**, 167–171.

DICKSTEIN S. S. and FRAME B. (1973) Urinary tract calculi after intestinal shunt operations for the treatment of obesity. *Surg. Gynecol. Obstet.* **136**, 257–260.

DRENICK E. J., SIMMONS F. and MURPHY J. F. (1970) Effect on hepatic morphology of treatment of obesity by fasting, reducing diets and small bowel bypass. *N. Engl. J. Med.* **282**, 829–834.

GALAPEAUX E. A., TEMPLETON R. D. and BORKON E. L. (1938) The influence of bile on the motility of the dog's colon. *Am. J. Physiol.* **121**, 130–136.

HOLLENBECK J. L., O'LEARY J. P., MAHER J. W. et al. (1975) An etiologic basis for fatty liver after jejunoileal bypass. *J. Surg. Res.* **18**, 83–89.

JEWELL W. R., HERMRECK A. S. and HARDIN C. A. (1975) Complications of jejunoileal bypass for morbid obesity. *Arch. Surg.* **110**, 1039–1042.

KINNEY J., GOLDWYN R. M., BARR J. S. jun. et al. (1962) Loss of the entire jejunum and ileum and the ascending colon. Management of a patient. *JAMA* **179**, 529–532.

KREMEN A. J., LINNER J. H. and NELSON C. H. (1954) An experimental evaluation of the nutritional importance of proximal and distal small intestine. *Ann. Surg.* **140**, 439–448.

MCCLELLAND R. N., DESHAZO C. V., HEIMBACH D. M. et al. (1970) Prevention of hepatic injury after jejunoileal bypass by supplemental jejunostomy feedings. *Surg. Forum.* **21**, 368–370.

MANN F. C. and WILLIAMSON C. S. (1923) The experimental production of peptic ulcer. *Ann. Surg.* **77**, 409–422.

MEKHJIAN H. S. and PHILLIPS S. F. (1970) Perfusion of the canine colon with unconjugated bile acids. Effect on water and electrolyte transport, morphology, and bile acid absorption. *Gastroenterology* **59**, 120–129.

MEKHJIAN H. S., PHILLIPS S. F. and HOFMANN A. F. (1968) Conjugated bile salts block water and electrolyte transport by human colon. *Gastroenterology* **54**, 1256 (Abstr.)

MEKHJIAN H. S., PHILLIPS S. F. and HOFMANN A. F. (1971) Colonic secretion of water and electrolytes induced by bile acids: perfusion studies in man. *J. Clin. Invest.* **50**, 1569–1577.

MEYER A. E. and MCEWEN J. P. (1948) Bile acids and their choline salts applied to the inner surface of the isolated colon and ileum of the guinea-pig. *Am. J. Physiol.* **153**, 386–392.

MEYER H. V. (1962) Sixteen-year survival following extensive resection of small and large intestine for thrombosis of superior mesenteric artery. *Surgery* **51**, 755–759.

O'LEARY J. P., THOMAS W. C. jun. and WOODWARD E. R. (1974) Urinary tract stone after small bowel bypass for morbid obesity. *Am. J. Surg.* **127**, 142–147.

OLIVER J. V. (1949) Effect of gastrectomy and diversion of duodenal secretions into the terminal portion of the ileum on development of ulcer. *Arch. Surg.* **59**, 199–209.

OLIVER J. V. (1951) Effects of vagus section with subtotal gastrectomy and diversion of duodenal secretions into terminal portion of ileum in ulcer development. *Arch. Surg.* **62**, 649–657.

SALMON P. A. (1971) The results of small intestine bypass operations for the treatment of obesity. *Surg. Gynecol. Obstet.* **132**, 965–979.

SCOPINARO N. (1974) Tavola rotonda su: trattamento medico-chirurgico della obesità grave. Intervento. *Accad. Med.* **88–89**, 215–234.

SCOPINARO N., MARUGO M., PANDOLFO N. et al. (1976) Comportamento della secrezione gastrica e dell'increzione gastrinica nell'obeso grave trattato con corto-circuito digiuno-ileale. *Minerva Chir.* **31**, 573–576.

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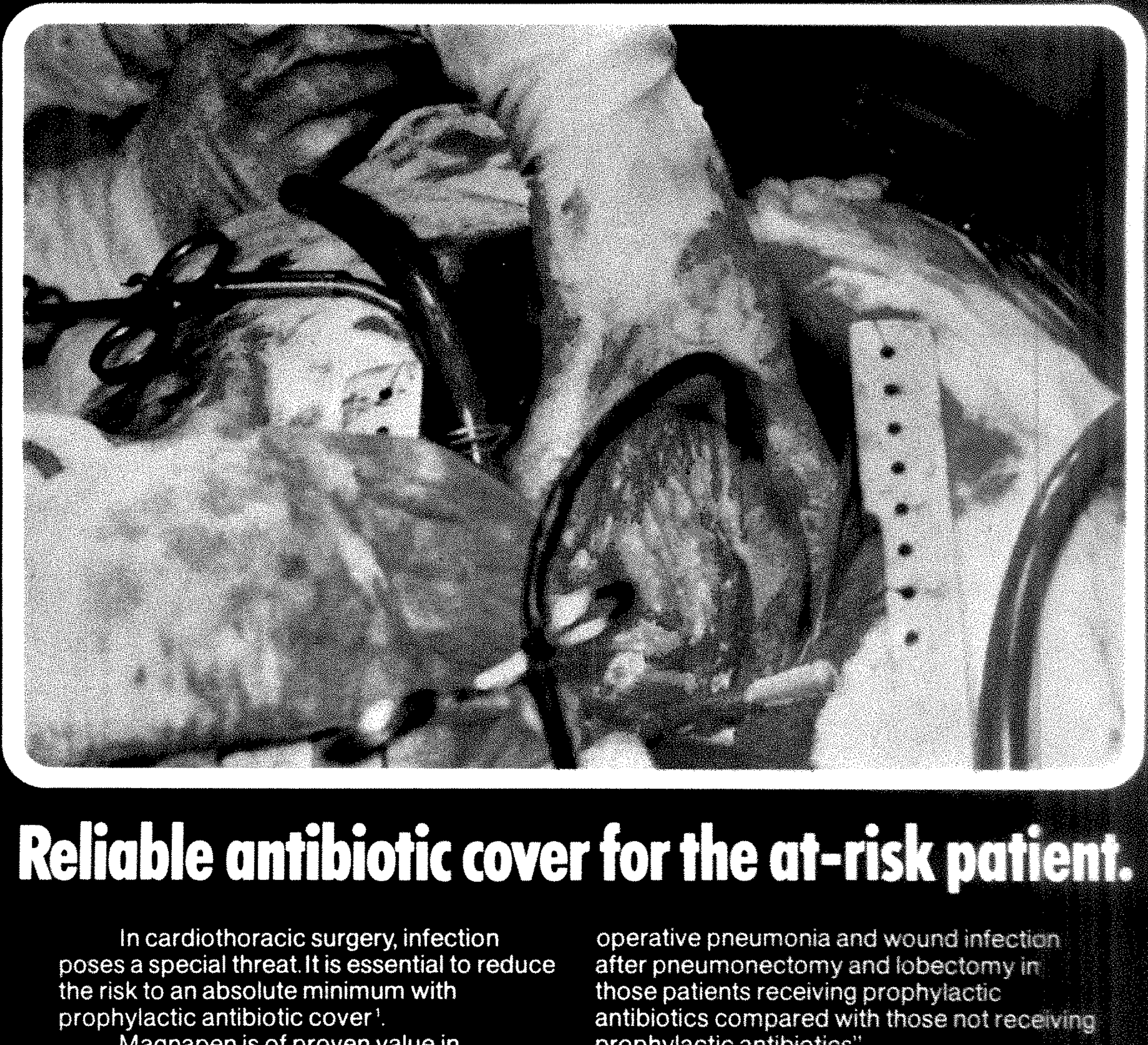

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2 Thorax (1978). 33, 1, 130
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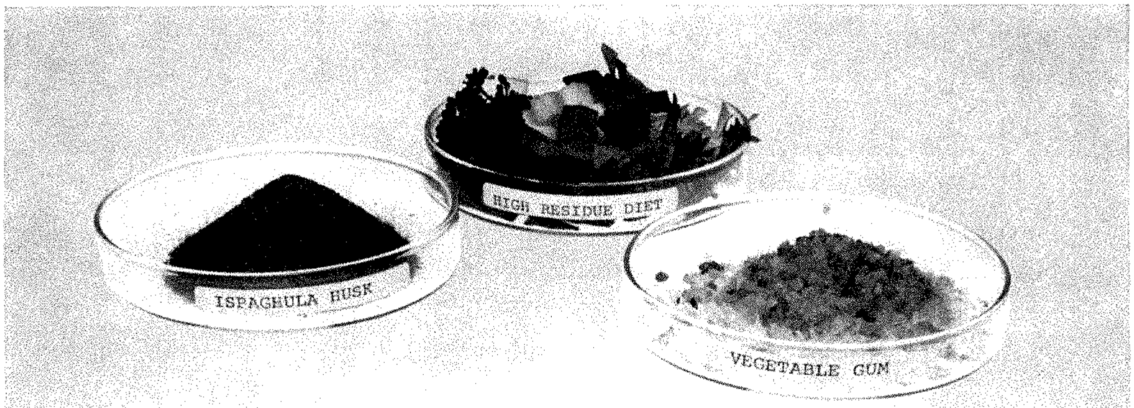

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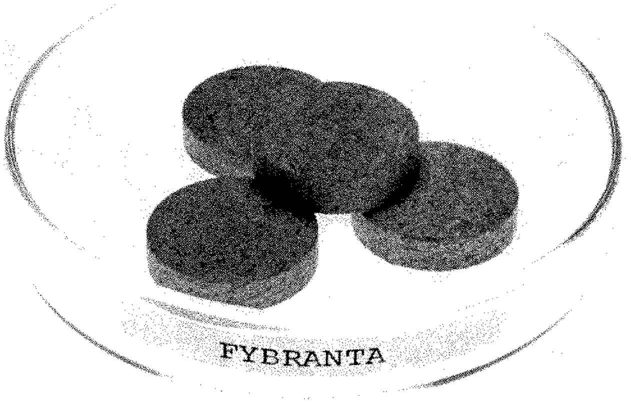

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SCOPINARO N., RODA E. and GIANETTA E. (1976) Aspetti patogenetici della litiasi biliare come complicanza del cortocircuito digiuno-ileale. *Minerva Chir.* 31, 567–572.

SHERR H. P., NAIR P. P., WHITE J. J. et al. (1974) Bile acid metabolism and hepatic disease following small bowel bypass for obesity. *Am. J. Clin. Nutr.* 27, 1369–1379.

SOLHAUG J. H. and SCHRUMPF E. (1976) Effect of small bowel bypass on serum gastrin levels and gastric acid secretion in man. *Scand. J. Gastroenterol.* **11**, 329, 332.

STORER E. H., WOODWARD E. R. and DRAGSTEDT L. R. (1950) The effect of vagotomy and antrum resection on the Mann–Williamson ulcer. *Surgery* 27, 526–530.

WISE L., BOUCHER J. K. and FEUTZ E. (1976) Intussusception following jejunoileal bypass: case report and review of the literature. *Am. Surg.* 42, 346–349.

WISE L. and STEIN T. (1975) Biliary and urinary calculi. Pathogenesis following small bowel bypass for obesity. *Arch. Surg.* **110**, 1043–1047.

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Bilio-pancreatic bypass for obesity: II. Initial experience in man

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SUMMARY

After a successful trial of bilio-pancreatic bypass in dogs, a clinical study has been completed in 18 patients followed for more than 1 year. The operation has been modified to achieve the best weight reduction, and forming the bilio-pancreatic tract of equal length to the alimentary tract with a short common ileal tract, the average weight loss as a percentage of the preoperative body weight was 24·1 ± 5·4 per cent (mean ± s.d.) at 6 months and 33·7 ± 4·1 per cent at 12 months. The only immediate complication was a wound dehiscence, and there were no late complications. Liver function studies showed the absence of hepatic deterioration and liver biopsies showed improvement of liver morphology 1 year after the operation. It is suggested that this procedure may be an alternative to jejuno-ileal bypass in the management of obesity.

THE operation of bilio-pancreatic bypass has been described in dogs (Scopinaro et al., 1979) and found to produce selective malabsorption with good weight loss. In this operation a partial gastrectomy is performed with closure of the duodenal stump. The jejunum is transected 20 cm distal to the ligament of Treitz and a gastrojejunostomy is performed using the distal part of the Roux loop. The proximal part of the jejunal loop is anastomosed to the distal ileum. The main feature of this arrangement is that the separate passage of aliments and bilio-pancreatic secretion in the distal ileum makes it possible to obtain a fat and starch maldigestion leaving the enterohepatic bile salt circulation undisturbed. Animal studies suggested that this procedure produces a selective rather than indiscriminate malabsorption, a slow rather than rapid recovery of absorptive function and no complications from an excluded intestinal loop. This study describes our experience with 18 patients who had this operation to treat gross obesity.

Patients and methods

Eighteen patients whose weight had been 45 kg above their ideal weight for the previous 5 years, and who had been recommended to have a weight-reducing operation, agreed to have a bilio-pancreatic bypass procedure after the experimental nature of the operation had been fully explained. Each patient had failed to reduce weight by non-operative methods and no medical cause for their obesity had been found. All patients were under 50 years of age and had no other disease which might increase the operative risk. All patients were emotionally stable and intelligent enough to understand the risk of the operation; all had agreed to cooperate in the studies and the prolonged follow-up. The details of the 18 patients are shown in *Table I*. The operative technique was essentially the same as that described in dogs (Scopinaro et al., 1979) with the following differences: in the first 3 patients a selective vagotomy was added to the gastrectomy; a retrocolic gastroentero-anastomosis was made in 10 patients; four types of operation were tested by varying the length of the three components of the small gut (*Fig.* 1). Four patients had a bilio-pancreatic bypass, with a bilio-pancreatic tract of 30 cm and a common ileal segment equivalent to either one-seventh or one-tenth of the small bowel total length (group I). Two patients had a bilio-pancreatico–jejunal bypass in which the jejunum was transected 100–200 cm from the ligament of Treitz and a one-seventh common ileal segment formed (group II). Five patients had a bilio-pancreatico–jejunal bypass in which the small intestine was divided at its mid point so that the entire jejunum was excluded and the bilio-pancreatic and the alimentary tracts were of equal length, while the common ileal segment was equivalent to either one-seventh or one-tenth of the small bowel total length (group III). Group IV patients ($n = 7$) had a bilio-pancreatico–jejunal bypass which was identical to group II except that the common ileal segment had a fixed length of 50 cm.

Table I: CLINICAL DETAILS OF 18 PATIENTS WHO UNDERWENT BILIO-PANCREATIC BYPASS

Sex	Age (yr)	Height (cm)	Weight (kg)	Follow-up (mth)
F	43	152	105·0	22
M	38	178	132·0	22
F	30	165	137·2	21
F	36	154	99·9	20
M	32	175	149·0	19
F	25	153	92·9	18
F	17	164	110·0	17
F	37	155	102·0	17
F	28	160	137·6	16
F	30	153	115·0	16
M	34	177	122·6	16
F	36	166	137·3	15
F	49	165	136·7	15
F	45	155	131·8	15
M	33	182	122·2	15
F	36	150	150·0	15
F	27	163	103·0	15
M	30	175	120·0	14
Mean	34	163·4	122·5	17

The patients were seen for at least 14 months after the operation and their weight loss was monitored. Blood studies, performed preoperatively and at 1, 4 and 12 months after the operation, included serum electrolytes, total protein and albumin, blood urea nitrogen, blood sugar, blood sedimentation rate, blood count and serum cholesterol. Liver function tests were performed preoperatively and at 1, 4 and 12 months after the operation. These tests included serum bilirubin, blood ammonia, serum alkaline phosphatase, bromsulphthalein retention test (BSP), thymol turbidity, serum fibrinogen, prothrombin time and SGOT and SGPT. In addition, a wedge biopsy of the liver was performed at the operation and subsequently percutaneous needle biopsies were carried out at 1, 4 and 12 months postoperatively.

Because of the resemblance of this operation to the Mann–Williamson procedure for the experimental production of an ulcer, basal acid output was determined preoperatively and at 1, 4 and 12 months after the operation. In order to be certain that a peptic ulcer was not developing, gastroscopy was performed at 4 and 12 months after the procedure. On each occasion a gastric mucosal biopsy was performed.

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Results

Recovery from the operation was quick and uneventful in all but one patient, who had a wound dehiscence which required resuture. No patient required dietetic or pharmacological management during the follow-up period. All patients had a normal appetite and, when left on a free diet after discharge from the hospital, rapidly returned to their preoperative eating habits with a calorie intake equal to or higher than before the operation. After return of bowel function and during the follow-up period patients passed an average of three to four soft to formed stools per day. No patient developed watery diarrhoea. Soon after discharge from hospital all patients were able to return to their normal occupations. The only complaint during the whole of the follow-up period was a transient anorectal irritation, complained of by 5 patients; this disappeared spontaneously during the second postoperative month.

Weight loss in group I (*n* = 4) was poor (*Fig.* 2) compared with the other groups. After bilio-pancreatico-jejunal bypass (groups II and III) the mean weight loss was 21·8 ± 4·3 per cent (mean ± s.d.) of the original weight at 6 months and 26·2 ± 2·6 per cent at 12 months (*Fig.* 3), while in group IV the weight loss was 24·1 ± 5·4 per cent and 33·7 ± 4·1 per cent at 6 and 12 months postoperatively (*Fig.* 4).

No patient showed any abnormality in serum electrolytes, total protein and albumin, blood urea nitrogen, blood sugar, blood sedimentation rate or blood count in the postoperative period.

One patient was hypercholesteraemic before operation. The average percentage reduction for the 18 patients from the preoperative cholesterol level was 18·8 ± 12·2 per cent at 1 month, 24·8 ± 11·8 per cent at 4 months and 35·0 ± 11·1 per cent at 12 months, with normalized values in the above-mentioned patient.

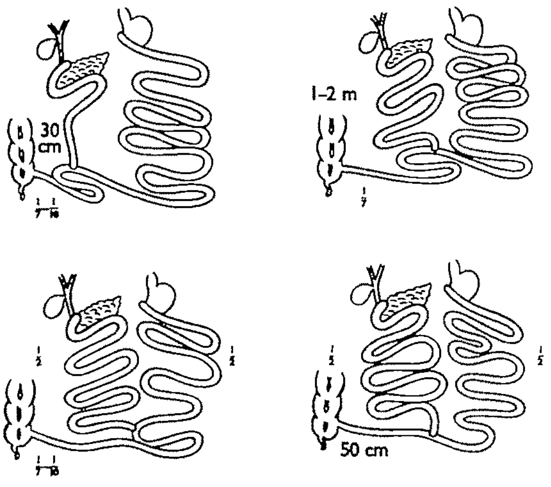

Fig. 1. The operative procedures performed in the 18 patients who had bilio-pancreatic bypass: *a*, group I (*n* = 4); *b*, group II (*n* = 2); *c*, group III (*n* = 5); *d*, group IV (*n* = 7).

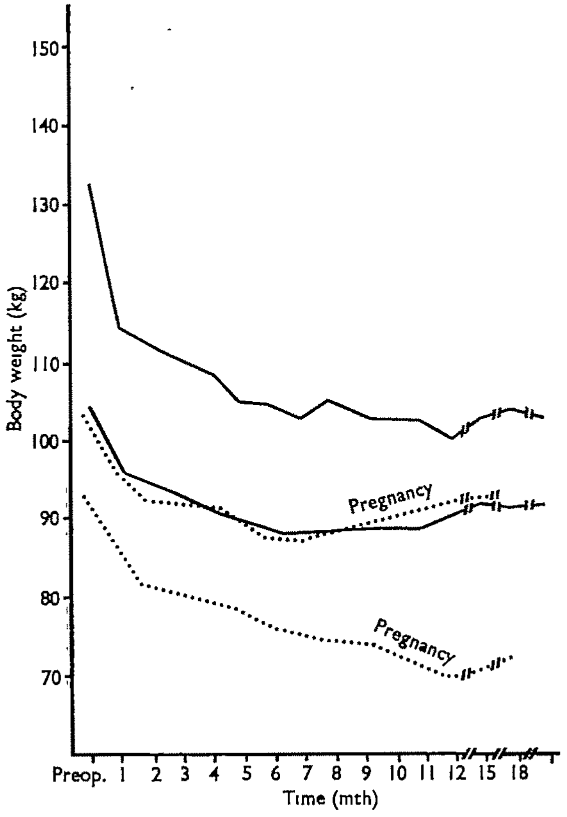

Fig. 2. The weight reduction of the 4 patients in group I who had a bilio-pancreatic bypass alone.

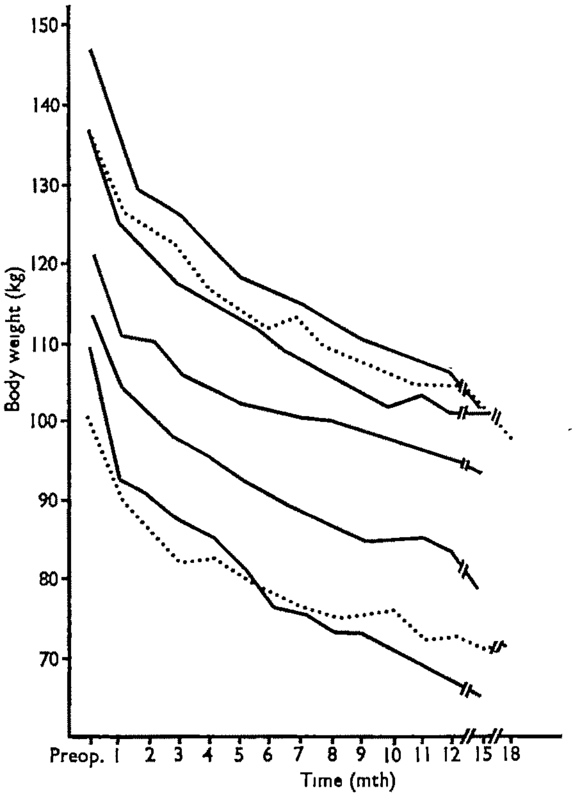

Fig. 3. The weight reduction of the 7 patients in groups II and III who had a bilio-pancreatico-jejunal bypass.

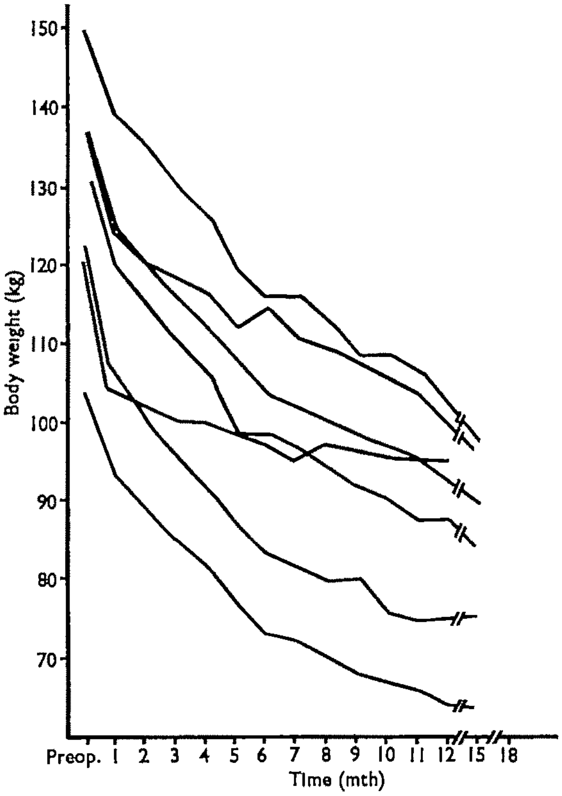

Fig. 4. The weight reduction in the 7 patients in group IV who had a bilio-pancreatico–jejunal bypass with a standard 50 cm common ileal segment.

Liver function tests revealed no change from the preoperative pattern at 1 and 4 months after the operation. As is common in obese subjects, there was an increase in the BSP retention in 12 of the 18 patients preoperatively and 5 patients had abnormal transaminase levels before operation. Twelve months after the operation there was a marked improvement in the liver function tests of those patients with abnormal preoperative studies. The wedge liver biopsy performed at operation demonstrated fatty metamorphosis and portal tract inflammation in 16 of the 18 patients. In the subsequent percutaneous needle biopsies of the liver an increase in fatty metamorphosis was never found. A striking improvement in liver morphology was observed in all the 12-month studies.

The mean reduction in basal acid output after bilio-pancreatic and bilio-pancreatico–jejunal bypass was 83 per cent at 1 month, 85 per cent at 4 months and 97 per cent at 12 months. The fall in basal acid secretion did not seem to be influenced by vagotomy. Gastroscopy showed a normal gastrojejunal anastomosis; the biopsies taken at the time of the gastroscopy showed no significant abnormality.

Discussion

The early experience of the use of bilio-pancreatic bypass confirms the experimental studies in dogs, namely that this procedure can be performed safely and without major complication. The absence of the negative effects which usually follow jejuno-ileal bypass is easily explained by the absence of the two main defects of the classic operation, that is: (*a*) the indiscriminate malabsorption, with the interruption of the enterohepatic bile salt circulation; (*b*) the long excluded intestinal loop (Scopinaro et al., 1979). The risk of a peptic ulcer occurrence at the gastrointestinal anastomosis appears unlikely, and this is undoubtedly due to the gastrectomy which is performed as part of this procedure.

In conclusion, it can be suggested that bilio-pancreatic diversion is an alternative clinical approach to jejuno-ileal bypass for the treatment of obesity The rate of weight loss appears to be more sustained in the patients with a shorter distance from the entero-enterostomy to the ileocaecal valve and with a longer jejunal loop excluded from the alimentary stream. However, the exact length of the common ileal segment and the length of jejunum in the bilio-pancreatic tract required to achieve maximum weight reduction with minimum complications have yet to be determined.

Reference

SCOPINARO N., GIANETTA E., CIVALLERI D. et al. (1979) Bilio-pancreatic bypass for obesity: I. An experimental study in dogs. *Br. J. Surg.* 66, 613–617.

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A 10-year survey of large bowel carcinoma at Groote Schuur Hospital with particular reference to patients under 30 years of age*

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SUMMARY

In a 10-year survey of large bowel carcinoma at Groote Schuur Hospital 926 cases were studied retrospectively. A marked difference was seen in both the age of presentation and histological differentiation in two different racial groups. All patients who were 29 years of age or less at the time of presentation have been studied in detail. Predisposing factors, symptomatology, treatment, pathology and prognosis are discussed. It is apparent that large bowel carcinoma in the young has a very poor prognosis.

THE geographical distribution and epidemiology of large bowel carcinoma are currently of great interest. Burkitt (1971) made a strong argument in favour of environmental and dietary carcinogens as a cause of this condition. The highest incidence appears to be in the Western world whereas low and very low incidences have been reported from Africa (Bremner and Ackerman, 1971; Ngala Kenda, 1976). The greatest incidence among both males and females is in Scotland. For males New Zealand is fourth and for females New Zealand is second (Enker, 1978). The purpose of the present study was to compare the features of carcinoma of the large bowel in two different groups; Caucasian patients and patients of mixed race, both living in the same area.

The Caucasians are descendants of immigrants from Holland, France, Britain and Germany who came to the Cape in the seventeenth and eighteenth centuries.

The group of mixed race are of diverse ethnic origins. They are descendants of the Hottentots (a primitive indigenous race of the Cape), slaves from West Africa and the East Indies, Caucasians and contract labourers from Malaya.

Patients and methods

Groote Schuur Hospital is a teaching hospital with 1380 beds serving patients of all races. The case reports of all patients admitted to the Hospital from June 1967 to June 1977 were reviewed and 941 cases of large bowel carcinoma were found, of which 926 gave adequate documentation for a retrospective study. Of these, 591 were Caucasians, 325 were of mixed race and only 10 were black. In view of their small number, black patients have been excluded from this study; this low figure can be explained on the basis of two factors. First, the disease is uncommon in this racial group (Bremner and Ackerman, 1971) and secondly the black population of Cape Town is considerably lower than that of other areas of South Africa.

Results

Age incidence

The ages of the Caucasian patients varied from 24 to 99 years, with the majority presenting in the seventh decade of life (median age 66 years). This is similar to the incidence in most Western series (Goligher, 1941).

The ages of the patients of mixed race ranged from 12 to 99 years, with the peak incidence in the fifth and sixth decades (median age 52 years).

It can be seen that there is a very striking difference in the median age of presentation between the two groups (*Fig.* 1). Other authors (El Masri and Boulos, 1975; Ngala Kenda, 1976) have also shown that non-Caucasian patients tend to present at an earlier age. In this study the difference cannot be explained on the basis of the mixed race population being younger than the Caucasian. The South African life tables show an almost identical life expectancy in the two groups after the age of 30 years (*Fig.* 2).

When reviewed by decades, 72 patients of mixed race (22·5 per cent) were 40 years of age or under, compared with 29 Caucasian patients (5 per cent) ($\chi^2 = 60$, $P < 0{\cdot}001$).

Eight per cent of the patients of mixed race were 29 years or under, a figure considerably higher than that given in any Western series (Rankin and Comfort, 1929; Pennington, 1963).

Sex incidence (*Table I*)

In the Caucasian patients the male to female ratio was 2 : 3 for colonic lesions, but 5 : 4 for rectal lesions, figures which correlate well with Western series (Smiddy and Goligher, 1957). Both sex ratios were reversed in the mixed race group and Bremner and Ackerman (1971) reported similar findings. They found that colonic carcinoma in South African blacks was more common in males than in females, whereas the incidence of rectal carcinoma was equally distributed between the sexes.

Anatomical distribution (*Table II*)

The anatomical distribution of the carcinoma by site in both race groups correlated well with most Western series (Smiddy and Goligher, 1957), with the exception of the high incidence of anal carcinoma in the mixed race group (5·5 per cent). However, Ngala Kenda (1976) from Zaire described the incidence of anal carcinoma as 10 per cent in blacks and El Masri and Boulos (1975) from the Sudan, reported a surprisingly high figure of 20 per cent in blacks. There appears to be no obvious explanation for this.

Synchronous lesions were seen in 2·8 per cent of Caucasian patients and 3·0 per cent of mixed race patients. These figures are similar to the incidence reported by most other authors (Goligher et al., 1951).

Pathological staging and differentiation

There was no statistical difference in the staging between the two groups, with the distribution being similar to most Western series (*Table III*). There was

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* Based on a paper presented at the 11th Biennial Congress of the Association of Surgeons of South Africa.

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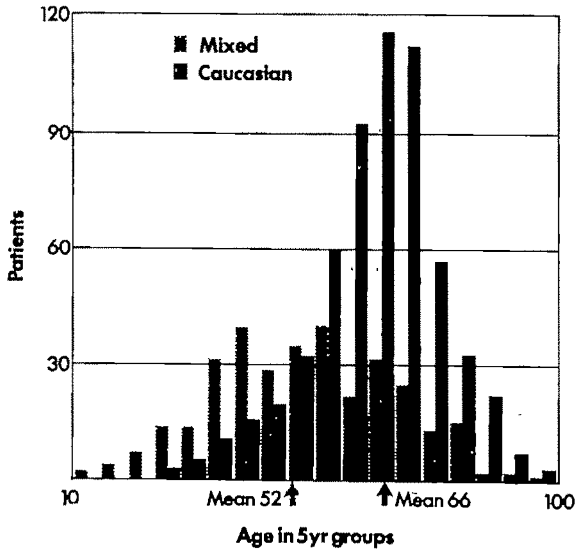

Fig. 1. Histogram showing ages of presentation in the two racial groups.

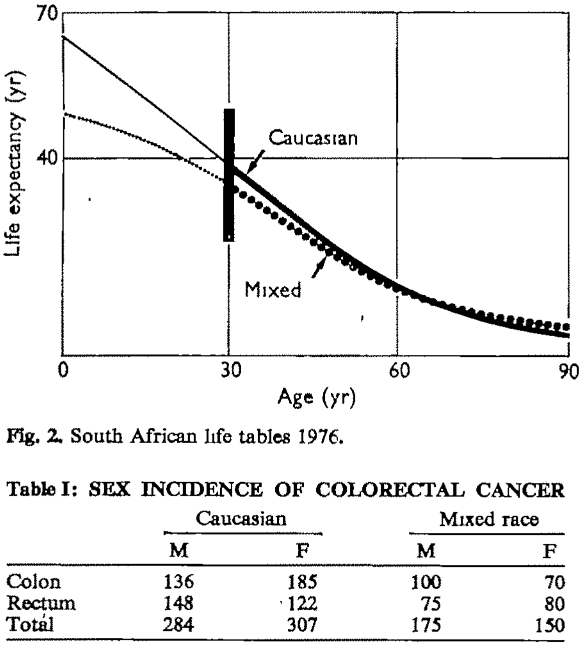

Fig. 2. South African life tables 1976.

Table I: SEX INCIDENCE OF COLORECTAL CANCER

	Caucasian		Mixed race	
	M	F	M	F
Colon	136	185	100	70
Rectum	148	122	75	80
Total	284	307	175	150

Table II: ANATOMICAL DISTRIBUTION OF LARGE BOWEL CANCER

	Caucasian (n = 591)	Mixed race (n = 325)
Caecum	12·4	11·4
Ascending colon	5·4	4·5
Hepatic flexure	2·5	4·2
Transverse colon	5·0	4·0
Splenic flexure	3·0	4·0
Descending colon	2·4	3·0
Sigmoid colon	22·0	20·0
Rectum	44·8	43·4
Anus	2·5	5·5

All figures are percentages.

a marked difference in the overall incidence of mucinous adenocarcinomas in the two groups—5 per cent of the Caucasians and 16 per cent of those of mixed race ($\chi^2 = 60$, $P<0{\cdot}001$). It is probable that at least part of the explanation for this is that the mixed race group were as a whole younger than the Caucasians. Davey (1968) found that mucinous carcinoma of the large bowel was particularly common in the African and this finding was supported by Ngala Kenda (1976), who found a 26 per cent incidence. However, again it would seem that the younger age group in these studies played an important role in the increased incidence.

Patients aged 19 years or less (*Table IV*)

There were 4 patients in this group, all of mixed race, with no family history or predisposing disease in any of them. The duration of symptoms varied from 3 days to 3 months. In 3 of the 4 patients the preoperative diagnosis was tuberculosis; the diagnosis in the fourth patient was acute appendicitis. In each case the tumour was resected and pathological examination showed all tumours to be mucus-forming lesions, indicating a very poor prognosis.

All patients were followed up until death and the longest survival time was 26 months.

Patients aged 20–29 years

There were 25 patients in this group of whom 22 were of mixed race and 3 Caucasian. There was no family history of bowel disease in any of the patients. None of the patients of mixed race had predisposing disease, whereas one Caucasian patient had long standing ulcerative colitis. The sex incidence and anatomical distribution were unremarkable, but the incidence of tumour resectability in this group was 42 per cent, compared with an overall figure of 82 per cent. The average duration of symptoms was 5 months, with a palpable mass being found in 64 per cent of cases.

Ten of this group of young patients (40 per cent) suffered a delay of between 1 and 18 months whilst investigations for suspected peptic ulcer disease were performed. Rectal examination would have revealed the diagnosis in 4 of these patients. The Dukes' pathological staging details are shown in *Table V* and histological differentiation in *Table VI*. The prognosis in general correlated more closely with the histological grading than with the pathological staging, full details of follow-up according to differentiation being shown in *Table VII*.

Discussion

Carcinoma of the colon and rectum is the most frequently diagnosed gastrointestinal malignancy regardless of age. Although it has been described in a stillborn (Ahfeld, 1880), the youngest documented patient was a 9-month-old girl (Kern and White, 1958). Approximately 1 per cent of all malignant growths of the large bowel are in persons under 30 years of age (Recio and Bussey, 1965; Hardin, 1972). According to some authors the prognosis of large bowel carcinoma is independent of age (Roth-Moyo et al., 1968; Hardin, 1972). However, our findings (*Fig.* 3) and those of other series (Recio and Bussey, 1965; Van Langenberg and Ong, 1972; Andersson and Bergdahl, 1976) would appear to refute this. In our series 88 per cent of patients under 30 years of age were of mixed racial origin. Chabalko and Fraumeni (1975) in the United

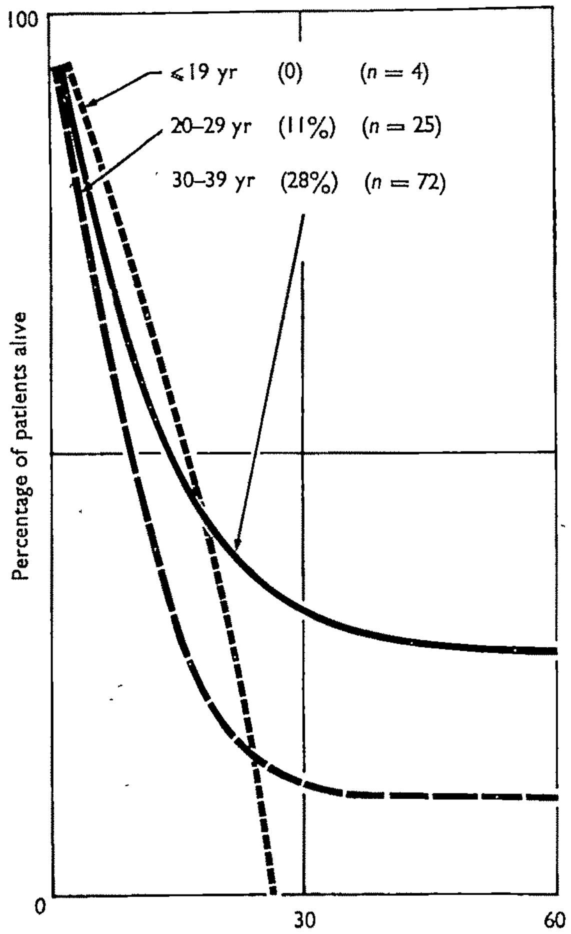

Fig. 3. Crude survival figures from 0 to 60 months for patients aged 12–39 years.

States also showed that the mortality from colorectal carcinoma in males under 20 years was four times higher amongst non-Caucasians than Caucasians.

None of our patients under 30 years of age had a family history of colorectal carcinoma. Van Langenberg and Ong (1972) likewise found no family history in 21 patients under 25 years of age.

The symptoms and their duration appear to be the same for young and old patients; however, in the younger age group the diagnosis of carcinoma is seldom entertained. Muir (1956) found that pain was a common feature with carcinoma of the right colon and that it tended to be situated in the epigastrium, with a definite relationship to meals, or to be located as pain in the appendicular region. This is supported by our finding that 10 of the 25 patients under 30 years of age were investigated for peptic ulcer disease for periods of 1 to 18 months before the correct diagnosis was made. One of our patients (S. B., *Table IV*), previously reported by Smith et al. (1976), underwent an emergency operation for abdominal pain. An appendicectomy was performed through a paramedian incision and the cause of the pain, a constricting carcinoma of the descending colon, was not detected. Many cases of large bowel carcinoma mimicking appendicitis have been recorded in children (Sessions et al., 1965; Andersson and Bergdahl, 1976). In these cases the symptoms are due to the increased intracolonic pressure which distends the caecum giving rise to localized tenderness in the right iliac fossa. It is therefore important if the history is at all atypical and the appendix is found to be normal at laparotomy that careful palpation of the colon and rectum be carried out.

In this series young patients had a very poor prognosis, with a lower incidence of resectability, despite a duration of symptoms similar to the other age groups (*Fig.* 3). This is largely due to the high incidence of mucin-forming tumours (*Table VI*); indeed all of our patients under 20 years of age had mucin-forming tumours. The incidence of mucin tumours appears to be higher than in similar age groups in Western populations (Coffey and Cardenas, 1964; Miller and Liechty, 1967). This would suggest that non-Caucasian

Table III: DUKES' PATHOLOGICAL STAGING

Stage	Caucasian ($n = 591$)	Mixed race ($n = 325$)
A	16	13
B	38	31
C	46	56

All figures are percentages.

Table IV: PATIENTS AGED 19 YEARS OR LESS

Case	Age/Sex (yr)	Site	Stage	Differentiation	Survival
S. B.	12/F	Desc. colon	B	Mucin: poor	Dead 26 mth
N. N.	13/M	Caecum	B	Mucin: mod.	Dead 24 mth
J. M.	18/M	Asc. colon	C_1	Mucin: poor	Dead 9 mth
V. P.	19/F	Caecum	C_2	Mucin: poor	Dead 1 yr

Desc., Descending; asc., ascending.

Table V: DUKES' PATHOLOGICAL STAGING ACCORDING TO AGE

Stage	0–19 yr ($n = 4$)	20–29 yr ($n = 25$)	30–40 yr ($n = 72$)
A	0	8	7
B	50	36	37
C	50	56	56

All figures are percentages.

Table VI: HISTOLOGICAL DIFFERENTIATION

	0–19 yr ($n = 4$)	20–29 yr ($n = 25$)	30–40 yr ($n = 72$)
Well/moderate	0	12	38
Poor	0	16	26
Mucin	100	72	36

All figures are percentages.

Table VII: FOLLOW-UP (PATIENTS AGED 20–29 YEARS)

2 well differentiated: alive at 7½ and 8 yr respectively
1 moderately differentiated: alive at 5 yr
4 poorly differentiated: all dead within 18 mth
18 mucin: 15 dead within 27 months
    1 alive at 14 mth (irresectable)
    1 alive at 6 mth (irresectable)
    1 alive at 4 mth (resected)

patients have a higher tendency to develop tumours of this type. Pillay et al. (1978) reviewed large bowel carcinoma in South African blacks under the age of 25; in all cases the tumours were shown to be mucus-forming. Middlekamp and Haffner (1963) reviewed microscopic sections of 27 published cases of carcinoma of the colon in children and found signet ring cells in 13 (47 per cent), i.e. ten times more frequently than in adult series, where the corresponding figure is 5 per cent (Hoerner, 1958).

When analysed by decades to 40 years there appeared to be only minimal differences in the Dukes' staging (*Table VI*). However, when the histological differentiation was reviewed there was a very dramatic change in the incidence of mucin-secreting carcinomas (*Table VI*). When the 5-year survival figures were reviewed, there was a very close correlation between tumour differentiation and 5-year survival. All our patients under 20 years had mucoid tumours and all were dead within 26 months. These depressing figures appear to be typical for this age group. Andersson and Bergdahl (1976) studied all published cases of large bowel carcinoma in children under 15 years and showed the 5-year survival rate to be 2·5 per cent. All patients under 30 years with poorly differentiated or mucin-secreting tumours were dead within 5 years, whilst those with well or moderately differentiated tumours were all alive at 5 years.

Conclusions

Large bowel carcinoma in patients of mixed race under 30 years of age is not rare. There appears to be a very striking difference in the median age of presentation between Caucasian and mixed race patients. Any young patient with abdominal pain, rectal bleeding or change in bowel habit should be evaluated with this in mind. The extremely poor prognosis in the young is due to the high incidence of mucin and undifferentiated tumours.

Acknowledgements

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References

AHFELD F. (1880) Zur Casuistik der congenitalen Neoplasmen. *Arch. Gynaekol.* **16**, 135–139.

ANDERSSON A. and BERGDAHL L. (1976) Carcinoma of the colon in children: a report of six new cases. *J. Pediatr. Surg.* **11**, 967–971.

BREMNER C. G. and ACKERMAN L. V. (1971) Polyps and carcinoma of the large bowel in the South African Bantu. *Cancer* **26**, 991–999.

BURKITT D. P. (1971) Epidemiology of cancer of the colon and rectum. *Cancer* **28**, 3–13.

CHABALKO J. J. and FRAUMENI J. F. (1975) Colorectal cancer in children. *Dis. Colon Rectum* **18**, 1–3.

COFFEY R. J. and CARDENAS (1964) Cancer of the bowel in the young adult. *Dis. Colon Rectum* **7**, 491–492.

DAVEY W. W. (1968) *Companion to Surgery in Africa.* Edinburgh, Livingstone, p. 261.

EL MASRI S. H. and BOULOS P. B. (1975) Carcinoma of the large bowel in the Sudan. *Br. J. Surg.* **62**, 284–286.

ENKER W. E. (1978) *Carcinoma of the Colon and Rectum.* Chicago, Year Book, p. 310.

GOLIGHER J. C. (1941) The operability of carcinoma of the rectum. *Br. Med. J.* **2**, 393–397.

GOLIGHER J. C., DUKES C. E. and BUSSEY H. J. R. (1951) Local recurrences after sphincter-saving excisions for carcinoma of the rectum and rectosigmoid. *Br. J. Surg.* **39**, 199–211.

HARDIN W. J. (1972) Unusual manifestations of malignant disease of the large intestine. *Surg. Clin. North Am.* **52**, 287–298.

HOERNER M. T. (1958) Carcinoma of the colon and rectum under 20 years of age. *Am. J. Surg.* **96**, 47–53.

KERN W. H. and WHITE W. C. (1958) Adenocarcinoma in a 9-month infant. *Cancer* **11**, 855–857.

MIDDELKAMP J. N. and HAFFNER H. (1963) Carcinoma of the colon in children. *Pediatrics* **32**, 558–571.

MILLER F. E. and LIECHTY R. D. (1967) Adenocarcinoma of the colon and rectum in persons under 30 years of age. *Am. J. Surg.* **113**, 507–510.

MUIR E. G. (1956) The diagnosis of carcinoma of the colon and rectum. *Br. J. Surg.* **44**, 1–7.

NGALA KENDA J. F. (1976) Cancer of the large bowel in the African: a 15-year survey at Kinshasa University Hospital, Zaire. *Br. J. Surg.* **63**, 966–968.

PENNINGTON J. R. (1963) *Carcinoma of the Colon and Rectum.* Springfield, Ill., Thomas.

PILLAY S. P., ANGORN I. B. and BAKER L. W. (1978). Colorectal carcinoma in young black patients. A report of eight cases. *J. Surg. Oncol.* **10**, 125–132.

RANKIN F. J. and COMFORT M. W. (1929) Carcinoma of the rectum in young persons. *J. Tenn. Med. Assoc.* **22**, 37–40.

RECIO P. and BUSSEY H. J. R. (1965) The pathology and prognosis of carcinoma of the rectum in the young. *Proc. R. Soc. Med.* **58**, 789–791.

ROTH-MOYO L. A., DEVITT J. E. and BROWN F. N. (1968) The effect of age on the behaviour of carcinoma of the colon and rectum. *Dis. Colon Rectum* **11**, 420–422.

SESSIONS R. T., RIDDELL D. H., KAPLAN H. J. et al. (1965) Carcinoma of the colon in the first two decades of life. *Ann. Surg.* **162**, 279–284.

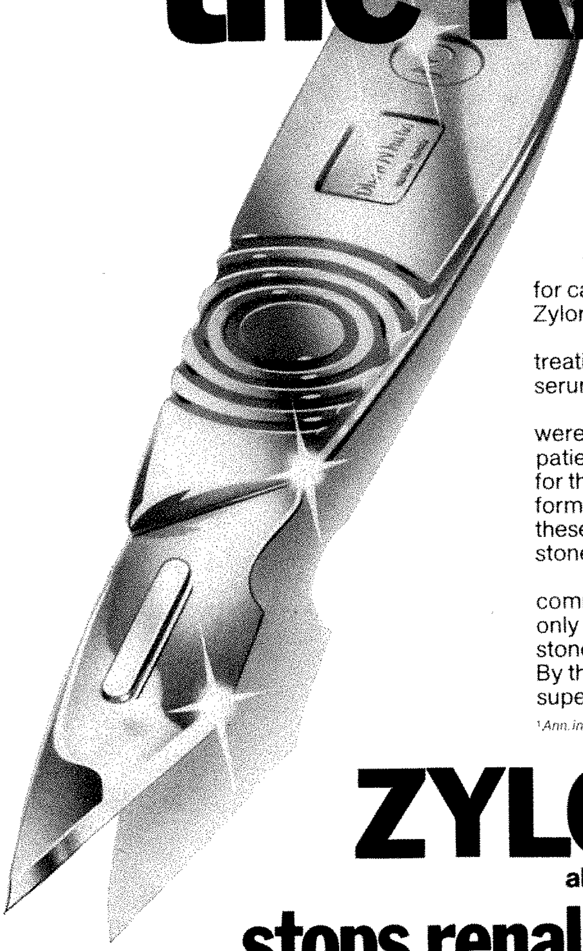
SMIDDY F. G. and GOLIGHER J. C. (1957) Results of surgery in the treatment of cancer of the large intestine. *Br. Med. J.* **1**, 793–797.

SMITH M. A. P., GOLDING R. L. and KATZ A. (1976) Carcinoma of the colon in a child. *S. Afr. Med. J.* **50**, 879–880.

VAN LANGENBERG A. and ONG G. B. (1972) Carcinoma of the large bowel in the young. *Br. Med. J.* **3**, 374–376.

Paper accepted 11 April 1979.

mightier than the knife



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[1] *Ann. intern. Med.* (1977), **87**, 404. [2] *Brit. med. J.* (1977), **2**, 1302. [3] *J. Urol.* (1977), 117, 690.

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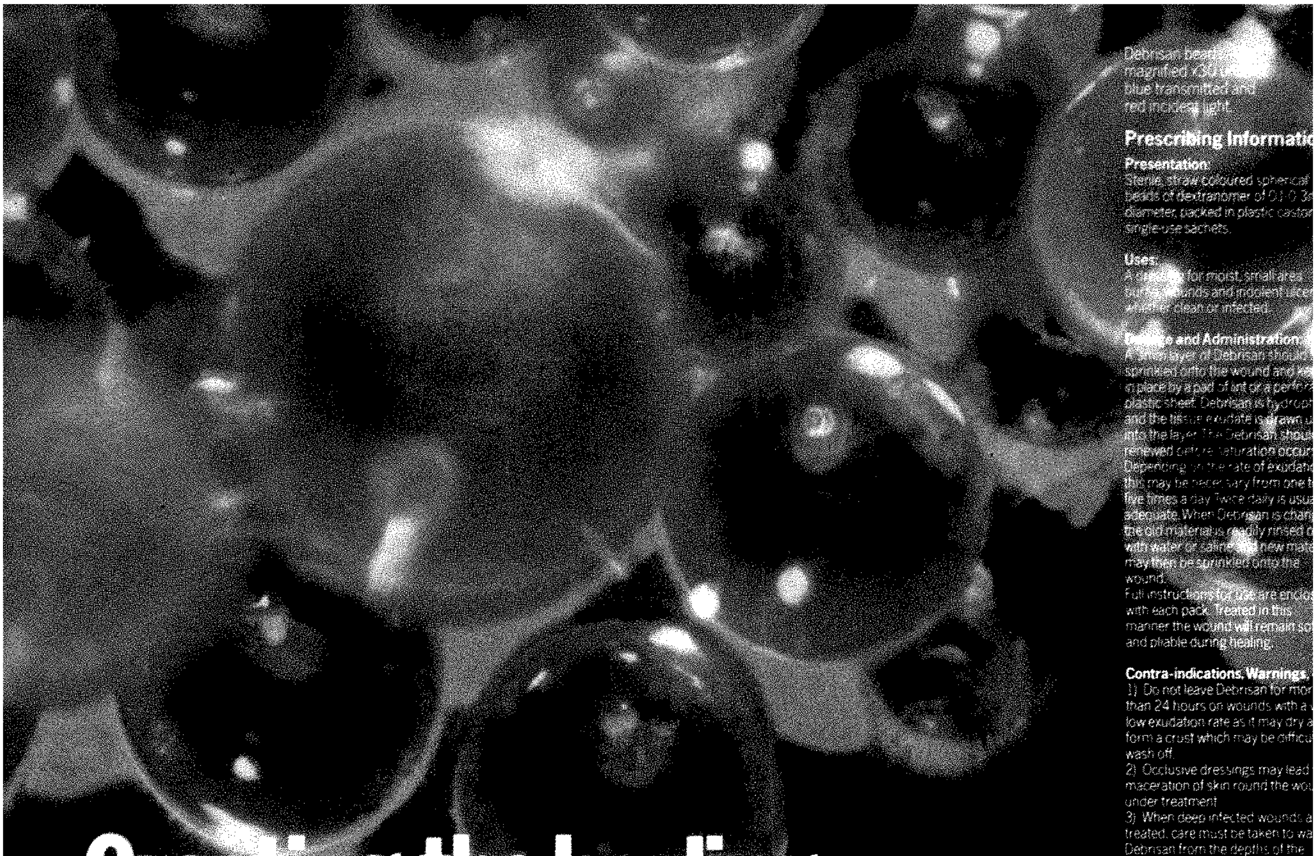

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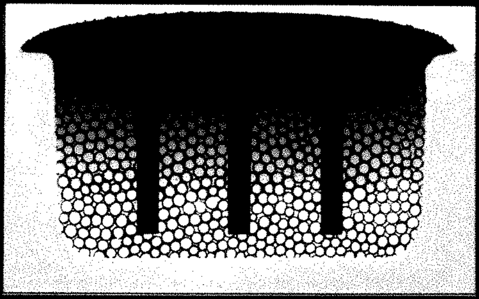

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Br. J. Surg. Vol. 66 (1979) 625–627

Total excision or restorative resection for carcinoma of the middle third of the rectum

R. J. NICHOLLS, JEAN K. RITCHIE, JANE WADSWORTH AND A. G. PARKS*

SUMMARY

Restorative resection is being used increasingly for carcinoma of the mid rectum but it is not yet certain whether this operation is as curative as total excision. Between 1963 and 1972, 209 patients left St Mark's Hospital after a radical operation for a single rectal carcinoma situated between 8 and 12 cm from the anal verge. A total of 199 patients was followed up for 5 years. Of these, 112 had been treated by total excision of the rectum and 87 by restorative operation. Survival was correlated with the Dukes' stage, histological grade and extent of local spread in the two groups.

There was no significant difference in 5-year survival after either total excision or restorative resection for Dukes' B (74 per cent, 71 per cent respectively) or average grade (61 per cent, 73 per cent respectively) tumours. Patients with Dukes' C tumours fared better when treated by restorative resection (36 per cent, 63 per cent), probably due to fewer high grade tumours in the restorative group (38 per cent, 18 per cent). Combining two variables, survival was not significantly different for patients with Dukes' B tumours of average grade (69 per cent, 62 per cent) or for Dukes' C tumours of average grade (48 per cent, 76 per cent). When the three pathological variables were combined, there was an improved survival after restorative resection for some pathological combinations.

It is concluded that restorative resection for carcinoma of the mid rectum is as curative as total excision in terms of 5-year survival.

THIRTY years ago total excision of the rectum was the accepted treatment for rectal carcinoma. During the 1940s, resection with restorative anastomosis began to be established as an alternative (Dixon, 1948; Lloyd-Davies, 1948; Mayo and Fly, 1956) and has since been used increasingly for growths of the upper rectum (Lockhart-Mummery et al., 1976). Since 1973 less than half of the patients undergoing operation for rectal carcinoma at St Mark's Hospital have required a permanent colostomy. This is largely because the scope of restorative resection has been extended to include tumours of the middle and occasionally of the lower third of the rectum. It is important to know whether these operations are as curative as rectal excision for tumours at these sites. For upper rectal tumours, Glenn and McSherry (1966) found that the 5-year survival rate with anterior resection was as good as with excision, but there is no evidence that this is true for tumours at lower levels.

In this retrospective study the results—expressed by 5-year survival rates—were compared in patients with carcinoma of the mid rectum treated either by rectal excision or by restorative procedures. Since, however, there is a tendency for more locally extensive and more undifferentiated tumours to be treated by excision (Slanetz et al., 1972; Lockhart-Mummery et al., 1976), overall results would be biased in favour of resection. Using Dukes' classification, histological grading and the extent of local spread of the tumour, the 5-year survival rates following one or other type of operation were therefore compared for patients in whom the tumours showed similar pathological features.

Patients and methods

The records of all patients admitted to St Mark's Hospital with operable carcinoma of the rectum between 1963 and 1972 were examined. Patients were included in the study—provided they survived the first 28 days postoperatively—if the lower edge of the tumour on sigmoidoscopy was between 8 and 12 cm from the anal verge and if the operation was a radical procedure (i.e. a clinical decision was made at operation that all known growth had been removed). Patients treated by local excision of the tumour and those with ulcerative colitis or adenomatous polyposis were excluded. Patients who had had a second malignant tumour in the bowel or elsewhere either synchronously or metachronously and those in whom 5-year survival could not be established (10 patients) were also excluded. With these criteria, 199 patients were available for study—112 treated by total excision of the rectum and 87 by a restorative resection (including 6 in whom the anastomosis was carried out peranally).

A simple form suitable for computer analysis was designed recording clinical and pathological variables relating to sex, age, Dukes' classification, histological grading, extent of local spread, longitudinal measurement and outcome at 5 years. The cause of death was classified as due to carcinoma or unrelated cause; when the cause was unknown (14 patients) death was assumed to be due to carcinoma. (The patients shown as dead in *Tables III–VII* are those in whom death was due to carcinoma or unknown cause.) All results were analysed in the two groups. The significance of the contingency tables was assessed by the χ^2 test or by Fisher's exact test where appropriate and differences in age were assessed by Student's t test.

Results

Clinical attributes (Table I)

There was no significant difference in the sex distribution in the two groups but the mean age was significantly higher in the restorative resection group.

Pathological attributes (Table II)

The distribution of the Dukes' classification, histological grade and extent of local spread was significantly different between patients treated by total excision and those undergoing restorative resection. The mean longitudinal measurement of the tumour on the specimen was 5·0 cm in the former group and 4·8 cm in the latter. These figures were not significantly different.

Survival

The overall 5-year survival in the two groups is shown in *Table III*. A significantly higher proportion of patients treated by restorative resection survived 5 years. The women particularly showed this outcome, in the men it was less marked.

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* St Mark's Hospital, London. Jane Wadsworth, Department of Medical Electronics, St Bartholomew's Hospital, London.

Table I: COMPARISON OF CLINICAL ATTRIBUTES IN THE TWO GROUPS

	No. of patients	Male	Female	Mean age (yr)
Total excision	112	75 (67%)	37 (33%)	60·2 (s.d. 10·89)
Restorative resection	87	48 (55%)	39 (45%)	63·4* (s.d. 9·68)

* $P<0{\cdot}05$, Student's *t* test.

Table II: PATHOLOGICAL ATTRIBUTES IN THE TWO GROUPS

	Total excision ($n = 112$)	Restorative resection ($n = 87$)
Dukes' classification		
A	11 (9·8)	18 (20·7)
B	46 (41·1)	41 (47·1)
C_1	45 (40·2)	25 (28·7)
C_2	10 (8·9)	3 (3·4)
Histological grading		
Low	23 (20·5)	21 (24·1)
Average	65 (58·1)	61 (70·1)
High	24 (21·4)	5 (5·7)
Extent of local spread		
Nil	12 (10·7)	21 (24·1)
Slight	35 (31·3)	34 (39·1)
Moderate	25 (22·3)	14 (16·1)
Extensive	40 (35·7)	18 (20·7)

Figures in brackets are percentages.

Table III: OVERALL 5-YEAR SURVIVAL: DEATH DUE TO CARCINOMA OR UNKNOWN CAUSE

	Dead	Alive	Total
Total excision	46 (43·4%)	60 (56·6%)	106†
Restorative resection	22 (27·2%)	59 (72·8%)*	81†

* $\chi^2 = 4{\cdot}55$, $P<0{\cdot}05$.
† Six deaths from unrelated causes.

Table IV: SURVIVAL RELATED TO TWO VARIABLES IN THE TWO GROUPS AMONG PATIENTS WITH DUKES' B AND C TUMOURS OF AVERAGE GRADE

	B average grade			C average grade		
	Dead	Alive	Total	Dead	Alive	Total
Total excision	8	18	26	15	14	29
Restorative resection	10	16	26	5	16	21

Differences are not significant.

Table V: FIVE-YEAR SURVIVAL OF DUKES' B CASES OF LOW OR AVERAGE GRADE AND NIL OR SLIGHT SPREAD IN THE TWO GROUPS

	Dead	Alive	Total
Total excision	5	11	16
Restorative resection	1	20	21

$P<0{\cdot}05$, Fisher's exact test.

Table VI: FIVE-YEAR SURVIVAL OF DUKES' C CASES OF LOW OR AVERAGE GRADE AND SLIGHT OR MODERATE SPREAD IN THE TWO GROUPS

	Dead	Alive	Total
Total excision	12	12	24
Restorative resection	2	13	15

$\chi^2 = 3{\cdot}92$, $P<0{\cdot}05$.

Table VII: FIVE-YEAR SURVIVAL OF DUKES' C CASES OF LOW OR AVERAGE GRADE AND MODERATE OR EXTENSIVE SPREAD IN THE TWO GROUPS

	Dead	Alive	Total
Total excision	10	6	16
Restorative resection	1	8	9

$P<0{\cdot}05$, Fisher's exact test.

Single variables: When *Dukes' classification* was studied there was no difference in survival for the Dukes' A (total excision 10/11, restorative resection 15/16) or B cases (total excision 31/42, restorative resection 27/38). For C cases, a significantly higher proportion of those treated by restorative resection were alive at 5 years; 17 out of 27 treated by restorative resection survived compared with 19 out of 53 treated by total excision ($\chi^2 = 4{\cdot}27$, $P<0{\cdot}05$).

There was no significant difference in survival between patients treated by either type of operation for any *grade of histology*; in particular survival rates were similar for patients with average grade tumours (total excision 37 out of 61, restorative resection 41 out of 56).

Survival was similar for total excision and restorative resection for patients with each of the *extents of spread*.

Two variables: Sufficient numbers of patients with Dukes' B tumours of average grade and Dukes' C of average grade were available for analysis. The 5-year survival in each of these categories was not significantly different for total excision or restorative resection (*Table IV*).

It was necessary to group the categories of spread to obtain sufficient numbers. Of all the analyses carried out involving Dukes' classification and spread, or histology and spread, the only group that showed a significant difference in survival between total excision and restorative resection was Dukes' B with slight or moderate spread. Survival was significantly better in the restorative resection group; 28 out of 34 survived compared with 24 out of 41 treated by total excision ($\chi^2 = 3{\cdot}9$, $P<0{\cdot}05$).

Three variables: To define the subgroups more exactly it was important to include all three variables to detect differences in survival. This resulted in small subgroups. There were significant differences in survival in some of the combinations. *Tables V, VI and VII* show that in selected groups patients treated by restorative resection fared better than those treated by total excision; in no instance was the reverse true.

Discussion

It is technically feasible to perform a restorative operation for some growths only a few centimetres above the anorectal ring, either by some form of pull-through procedure (Babcock, 1939; Bacon, 1956; Cutait and Figliolini, 1961; Turnbull and Cuthbertson, 1961) or by peranal anastomosis (Parks, 1972). These techniques, together with anterior resection, enable most rectal tumours to be treated by restorative procedures. It is essential to compare survival in these patients with those treated by excision. Prognosis depends largely on the pathological nature of the tumour. When attempting to compare the results of the two types of treatment the pathological features must be taken into account.

It has been maintained that the 5-year survival rate after restorative operations for carcinoma of the mid or upper rectum is similar to that obtained by complete rectal excision (Waugh et al., 1955; Palumbo and Sharpe, 1968). In these reports, however, there was no clear definition of the Dukes' stage, histological grade or extent of local spread of the tumours. It is quite possible that the more advanced and poorly differentiated tumours tend to be treated by total excision and the less advanced by restorative resection (Slanetz et al., 1972; Lockhart-Mummery et al., 1976). This bias is evident in the data presented in this study and, if not allowed for, would result in a possibly spurious advantage in favour of restorative resection. Attempts have been made to compare the results of these two operations for tumours of similar pathological stage. Slanetz et al. (1972) reported 5-year survival rates of 27 per cent and 22 per cent for abdominoperineal excision and anterior resection respectively in men with Dukes' C carcinoma between 8 and 18 cm from the anal verge. The corresponding figures for women were 52 per cent and 53 per cent. This analysis did not take the histological grade or the extent of local spread into consideration and the range of distances from the anal verge was too great for conclusions to be drawn about mid-rectal lesions. Glenn and McSherry (1966) determined the 5-year survival rates for patients with radically treated carcinoma of the rectum of Dukes' A, B and C stages lying above 10 cm from the anal margin. There was no statistical difference in survival after either anterior resection or rectal excision for tumours of the same Dukes' stage. Although other pathological features were not taken into account, this would suggest that the two operations produce similar results for tumours in the upper rectum.

In this study three different pathological features which influence prognosis were considered in comparing the results of excisional and restorative operations for carcinoma of the mid rectum. Ideally all the features should be combined, but this results in small numbers available for analysis. *Tables V*, *VI* and *VII* show that in certain subgroups patients with restorative resection fared better than those with total excision and in no case was the reverse true; however, it would be unwise to draw conclusions from such small numbers.

Comparison of survival in the two groups using only single variables may well lead to false conclusions. This is shown by the better survival of patients with Dukes' C tumours treated by restorative resection. This difference is very likely to be due to the greater proportion of high grade tumours in the Dukes' stage C total excision group (38·2 per cent compared with 17·9 per cent).

About 36 per cent of all operable rectal tumours are Dukes' B cases and Dukes' C cases form about 50 per cent, while almost 60 per cent are of average grade (Lockhart-Mummery et al., 1976). The two-variable analysis using these attributes is therefore the most useful for clinical practice. For tumours of average grade, no significant difference in survival following total excision or restorative resection for either Dukes' B or C tumours has been shown.

It is not possible to comment from this study on survival after removal of high grade tumours since there were only 5 patients with such tumours in the resection group. This reflects the attitude of surgeons who regard a preoperative biopsy showing a high grade tumour as an indication for total excision.

We conclude that for the most commonly occurring tumours in the mid rectum, i.e. Dukes' stage B or C tumours of average grade, the 5-year survival is similar after either total excision or restorative resection.

References

BABCOCK W. W. (1939) Experiences with resection of the colon and the elimination of colostomy. *Am. J. Surg.* **46**, 186–203.

BACON H. E. (1956) Abdominoperineal proctosigmoidectomy with sphincter preservation. Five-year and ten-year survival after pullthrough operation for cancer of the rectum. *JAMA* **160**, 628–634.

CUTAIT D. E. and FIGLIOLINI F. J. (1961) A new method of colorectal anastomosis in abdominoperineal resection. *Dis. Colon Rectum* **4**, 335–342.

DIXON C. F. (1948) Anterior resection for malignant lesions of the upper part of the rectum and the lower part of the sigmoid. *Ann. Surg.* **128**, 425–442.

GLENN F. and MCSHERRY C. K. (1966) Carcinoma of the distal large bowel: 32-year review of 1026 cases. *Ann. Surg.* **163**, 838–849.

LLOYD-DAVIES O. V. (1948) Radical excision of carcinoma of the rectum with conservation of the sphincters. *Proc. R. Soc. Med.* **41**, 822–827.

LOCKHART-MUMMERY H. E., RITCHIE J. K. and HAWLEY P. R. (1976) The results of surgical treatment for carcinoma of the rectum at St Mark's Hospital from 1948 to 1972. *Br. J. Surg.* **63**, 673–677.

MAYO C. W. and FLY O. A. (1956) Analysis of five-year survival in carcinoma of the rectum and rectosigmoid. *Surg. Gynecol. Obstet.* **103**, 94–100.

PALUMBO L. T. and SHARPE W. S. (1968) Anterior versus abdominoperineal resection. Resection for rectal and rectosigmoid carcinoma. *Am. J. Surg.* **115**, 657–660.

PARKS A. G. (1972) Transanal technique in low rectal anastomosis. *Proc. R. Soc. Med.* **65**, 975–976.

SLANETZ C. A., HERTER F. P. and GRINNELL R. S. (1972) Anterior resection versus abdominoperineal resection for cancer of the rectum and rectosigmoid. *Am. J. Surg.* **123**, 110–117.

TURNBULL R. B. and CUTHBERTSON A. (1961) Abdominorectal pullthrough for cancer and for Hirschsprung's disease. *Cleve. Clin. Q.* **28**, 109–115.

WAUGH J. M., BLOCK M. A. and GAGE R. P. (1955) Three- and five-year survivals following combined abdominoperineal resection, abdominoperineal resection with sphincter preservation and anterior resection for carcinoma of the rectum and lower part of the sigmoid colon. *Ann. Surg.* **142**, 752–757.

Paper accepted 26 March 1979.

Br. J. Surg. Vol. 66 (1979) 628–629

The results of vaginoplasty in excision of the rectum

GEORGE W. JOHNSTON*

SUMMARY

Vaginoplasty was used in a consecutive series of 45 patients undergoing rectal excision for neoplastic and inflammatory bowel disease. Forty-three patients achieved primary perineal healing and none developed a persistent perineal fistula.

One patient with Crohn's disease developed a perianal fistula a year after operation but healing occurred after minor surgery. Another developed a pre-sacral abscess 9 years after operation; spontaneous discharge into the vagina occurred.

MODERN colostomy and ileostomy appliances, coupled with the expertise of the stoma care nurse and the advice of self-help associations, have combined to reduce the problem of the artificial anus. Success in this area has focused more attention on the unsolved problem of the persistent perineal sinus. Ten years ago we described the operation of vaginoplasty as a method of obtaining primary perineal healing following rectal excision in the female (Johnston, 1969) and this paper reports the results of 10 years' experience with the method.

Operative technique

The rectum is excised without excision of the coccyx; the posterior vaginal wall is left intact initially. In inflammatory disease any fistulous or sinus tracts require to be laid open. The posterior vaginal wall is divided in the midline from the introitus to the cervix and transverse cuts are then made at the posterior aspect of the cervix freeing rotational flaps. Bleeding from the vaginal wall is easily controlled by diathermy but a running suture is more effective for the cervical margin. The lateral flaps of vaginal wall are now sutured to the side walls of the cavity with interrupted catgut sutures. The posterior fibro-fatty tissue is approximated with interrupted catgut sutures, building up the basis for the new posterior vaginal wall, and finally the skin wound is completely closed right up to the introitus. No perineal drainage tubes are necessary, the pelvic space draining freely through the newly constructed vagina. Actually the rotational flap grafts cover much of the raw cavity left by excision of the rectum, thereby reducing the volume of exudation and drainage.

Postoperatively the external dressing is changed as often as is required for the first couple of days and then daily irrigation of the vagina with eusol or saline is commenced. Sutures can be removed in 7–10 days, by which time the patient should be ready for daily baths. Over the next few weeks vaginal epithelium covers the small raw area on the newly constructed posterior vaginal wall. The patient may be allowed home 2 or 3 weeks after surgery with instructions to take daily baths and to wear merely a sanitary pad until any remaining discharge ceases; there is no need for the services of a district nurse. At the follow-up clinic a few months later the posterior vaginal wall is usually completely re-epithelized and the anterior perineum is virtually indistinguishable from normal.

Results

Obviously vaginoplasty is applicable only in the female patient, but it has been employed whether the rectal excision was required for cancer of the rectum or inflammatory disease of the large bowel. However, when a neoplasm involved the anterior rectal wall adjacent to the vagina, we routinely excised the whole of the posterior vaginal wall with the specimen thereby preventing the possibility of vaginoplasty; this group of patients was therefore excluded. This left a small personal consecutive series of 45 women treated by vaginoplasty at the time of rectal excision in the 10-year period under review. No patient was excluded because of perianal fistula, perineal sepsis, operative contamination or excess bleeding. Thirty patients had rectal excision for cancer, 9 for Crohn's disease, 5 for ulcerative colitis and 1 for an extensive villous papilloma. The patients' ages ranged from 22 to 90 (average 68). There were no operative deaths in the series. Primary healing of the perineal skin wound occurred in 43 of the 45 patients. In 2 elderly patients, one with a hemiplegia, the perineal wounds broke down on removal of the sutures, but fortunately both healed completely with simple secondary suture. No patient developed a pelvic or perineal abscess and there was no incidence of persistent perineal sinus formation. Although some patients left hospital within 2 weeks of operation the average postoperative hospital stay was 24 days, which is satisfactory considering the high average age of the group.

Further perineal problems occurred in only 2 patients. Both achieved primary perineal healing in spite of multiple preoperative perineal fistulas of Crohn's origin. More than 1 year after surgery one patient developed septic perineal sinuses which tracked subcutaneously and eventually produced a small fistula between the vagina and the perineum. This was resolved by further minor surgery. The other patient developed a small painful pre-sacral abscess 9 years after surgery. The abscess spontaneously discharged into the vagina, relieving the patient's symptoms and allowing resumption of normal sexual intercourse.

Discussion

Primary closure of the perineal wound was pioneered by Crile and Robnett (1950), who reported 78 per cent primary healing in patients with rectal cancer. Few have been able to better their results in spite of advances in bowel preparation, antibiotic therapy, drainage methods etc. (*Table I*). In inflammatory bowel disease the results are more depressing: primary healing of the perineal wound can be anticipated in only about 40 per cent of patients (*Table II*). Indeed, over 40 per cent may still have persistent perineal sinuses 6 months after surgery (*Table II*). About one-quarter of patients remain unhealed after 1 year and the majority of these are subjected to further surgery, although often little is accomplished by secondary operations.

It is generally agreed that the two major factors leading to perineal wound infection and subsequent sinus formation are operative contamination and inadequate drainage of the pelvic space. Frequently, in inflammatory bowel disease, pre-existing perineal sepsis makes operative contamination inevitable. In addition, the friable bowel is very susceptible to

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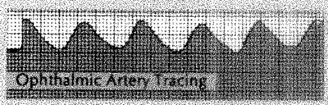

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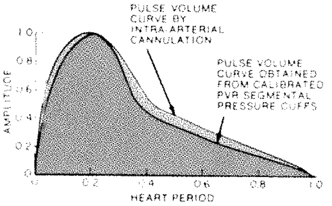

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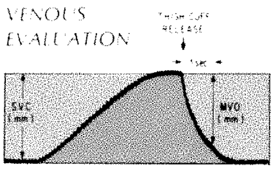

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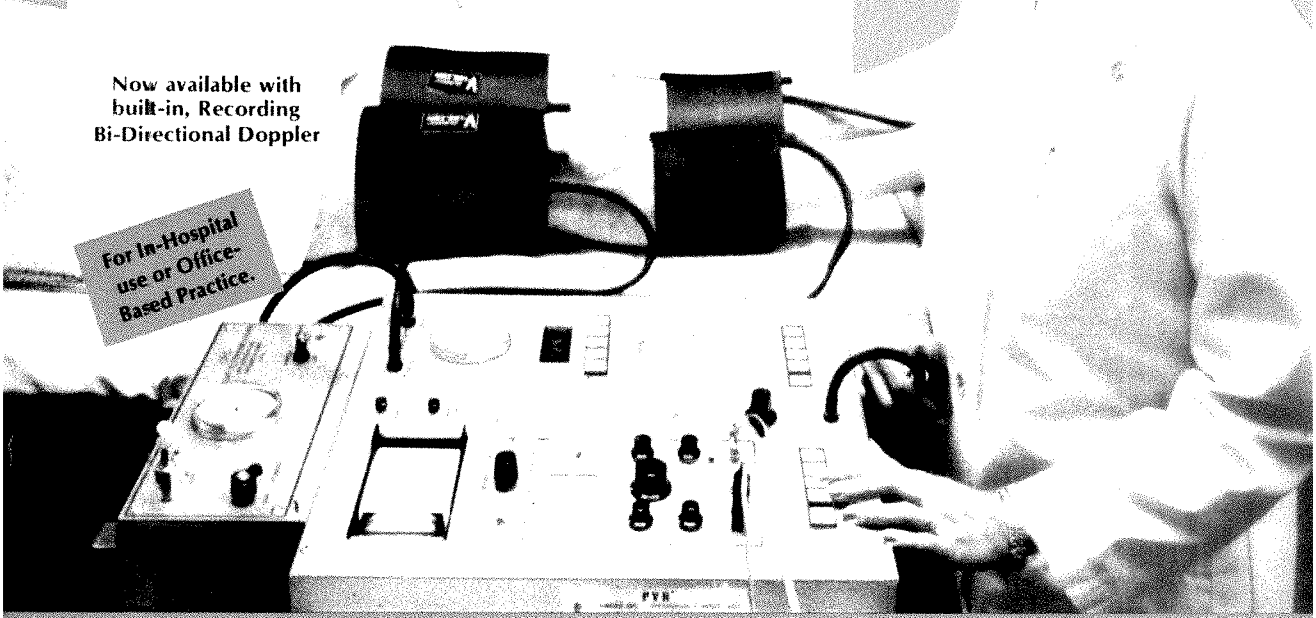

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1) Schneider et al., Chirurg **47,** 185 (1976)
2) McMichan et al., Med. Welt **27,** 2331 (1976)

Table I: THE PERINEAL WOUND IN CARCINOMA

Authors	No. of patients	Primary perineal healing (%)
Crile and Robnett (1950)	23	78
Altemeier et al. (1974)	129	91
Broader et al. (1974)	52	67
Kronborg et al. (1974)	150	37
Irvin and Goligher (1975)	33	45
Marks et al. (1976)	63	56
Saha and Robinson (1976)	41	88
Total	491	74

Table II: THE PERINEAL WOUND IN INFLAMMATORY DISEASE

Authors	No. of patients	Primary healing (%)	Unhealed at 6 mth (%)	Unhealed at 1 yr (%)
Watts et al. (1966)	93	—	25	27
Strahan et al. (1967)	45	20	58	27
Janlan et al. (1969)	106	—	55	37
Hultén et al. (1971)	29	72	—	—
Ritchie (1971)	157	—	49	23
Broader et al. (1974)	54	59	—	17
Irvin and Goligher (1975)	53	32	32	—
Marks et al. (1978)	76	43	—	18
Allsop and Lee (1978)	58	27	28	17
Total	671	41	42	24

damage, especially from traction by either the abdominal or perineal operator. The advantage of vaginoplasty is that such contamination does not preclude primary perineal suturing since the pelvis and perineum continue to drain freely through the newly constructed vagina. This prevents the formation of pelvic haematomas and thus minimizes the possibility of closed sepsis. Primary healing of the perineal wound is the rule rather than the exception.

In the past there has been a reluctance on the part of general surgeons to interfere with the vagina for fear of impairing vaginal function. However, Professor Goligher found that even after excision of the whole posterior vaginal wall in patients with rectal cancer the functional result was excellent (Goligher, 1967). By contrast, the operation of vaginoplasty sacrifices no vaginal tissue and amounts to little more than an episiotomy. In addition, the interference with muscle function of the organ differs little from that of routine rectal excision where the pelvic vaginal sphincter (the puborectalis muscle) is divided and the perineal vaginal sphincter (the bulbospongiosus muscle) rendered functionally useless by interference with the perineal body. In the present series, where vaginal function has been tested, both patients and husbands have reported no diminution in sexual satisfaction. In 1973 Hughes and Cuthbertson concluded 'there is no sure way of preventing the formation of a perineal sinus. It does not seem to be due to the manner in which the perineal wound is closed at operation.' Perhaps for the female, vaginoplasty provides the answer.

References

ALLSOP J. R. and LEE E. C. G. (1978) Factors which influenced postoperative complications in patients with ulcerative colitis or Crohn's disease of the colon on corticosteroids. *Gut* **19**, 729–734.

ALTEMEIER W. A., CULBERTSON W. R., ALEXANDER J. E. et al. (1974) Primary closure and healing of the perineal wound in abdomino-perineal resection of the rectum for carcinoma. *Am. J. Surg.* **127**, 215–219.

BROADER J. H., MASSELINK B. A., OATES G. D. et al. (1974) Management of the pelvic space after proctectomy. *Br. J. Surg.* **61**, 94–97.

CRILE G. and ROBNETT A. D. (1950) Primary closure of the posterior wound after combined abdominoperineal resection for cancer of the rectum. *Cleve. Clin. Q.* 17, 5–8.

GOLIGHER J. C. (1967) *Surgery of Anus, Rectum and Colon*, 2nd ed. London, Baillière, Tindall and Cassell, p. 701.

HUGHES E. S. R. and CUTHBERTSON A. M. (1973) *Ano-rectal Surgery*. Melbourne, McCarron Bird, p. 277.

HULTÉN L., KEWENTER J., KNUTTSON U. et al. (1971) Primary closure of perineal wound after proctocolectomy or rectal excision. *Acta Chir. Scand.* **137**, 467–469.

IRVIN T. T. and GOLIGHER J. C. (1975) A controlled clinical trial of three different methods of perineal wound management following excision of the rectum. *Br. J. Surg.* **62**, 287–291.

JANLAN K. N., SMITH A. N., RUCKLEY C. V. et al. (1969) Perineal wound healing in ulcerative colitis. *Br. J. Surg.* **56**, 749–753.

JOHNSTON G. W. (1969) A modification of the perineal dissection in excision of the rectum in females. *Br. J. Surg.* **56**, 530–532.

KRONBORG O., KRAMHOFT J., BACKER O. et al. (1974) Early complications following operations for cancer of the rectum and anus. *Dis. Colon Rectum* **17**, 741–749.

MARKS C. G., LEIGHTON M., RITCHIE J. K. et al. (1976) Primary suture of the perineal wound following rectal excision for adenocarcinoma. *Br. J. Surg.* **63**, 322–326.

MARKS C. G., RITCHIE J. K., TODD I. P. et al. (1978) Primary suture of the perineal wound following rectal excision for inflammatory bowel disease. *Br. J. Surg.* **65**, 560–564.

RITCHIE J. K. (1971) Ileostomy and excisional surgery for chronic inflammatory disease of the colon: a survey of one hospital region. *Gut* **12**, 528–540.

SAHA S. K. and ROBINSON A. F. (1976) A study of perineal wound healing after abdomino-perineal resection. *Br. J. Surg.* **63**, 553–558.

STRAHAN J., WILSON W. and MCMECHAN E. W. (1967) A review of surgically treated ulcerative colitis. *Ir. J. Med. Sci.* **494**, 83–88.

WATTS J. MCK., DEDOMBAL F. T. and GOLIGHER J. C. (1966) Long term complications and prognosis following major surgery for ulcerative colitis. *Br. J. Surg.* **63**, 1014–1023.

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Fulminating amoebic colitis: a clinical evaluation

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SUMMARY

Eleven cases of fulminating amoebic colitis seen in 5 years are reported. Only people of low socioeconomic status were affected and most were in good health previously. The disease appeared to follow a fulminant course from the onset and was rarely a secondary phenomenon superimposing on the chronic amoebic dysentery. The diagnosis was difficult due to severe systemic manifestations and the periodic absence of Entamoeba histolytica in the stool. The development of colonic necrosis was often masked by the severe pre-existing local signs and perforation could occur in spite of adequate anti-amoebic therapy. Mortality was related to late diagnosis, delayed recognition of irreversible colonic necrosis and inadequate surgical treatment.

To reduce the present 55 per cent mortality further it is proposed that, in an endemic area, early specific anti-amoebic therapy is justified in severe and undiagnosed colitis. Even under specific anti-amoebic treatment the patient with severe amoebic colitis remains a potential surgical candidate. Surgery is indicated when the patient continues to deteriorate in spite of the therapy, when there is an acute episode which signifies perforation, or when severe diarrhoea, toxaemia and abdominal tenderness persist after a full course of specific anti-amoebic therapy. Primary total resection of the diseased colon is the treatment of choice.

AMOEBIASIS is endemic in Thailand and amoebic colitis is normally a mild disease which responds well to medical treatment. Fulminating or necrotizing amoebic colitis is an unusual form of amoebic colitis characterized by severe toxaemia, rapid and extensive colonic necrosis and multiple perforations. Because of its rarity the disease is not generally recognized before irreversible colonic necrosis occurs and is almost invariably fatal. It is the purpose of this paper to present our experience in the diagnosis and management and to show that when surgical intervention is timely and adequate the prognosis of this once grave condition is vastly improved.

Patients and methods

From 1974 to 1978 inclusive 11 patients with fulminating amoebic colitis were treated in the surgical department, Chulalongkorn Hospital, Bangkok. The amoebic nature of the colitis was confirmed by the demonstration of *Entamoeba histolytica* in the stools or in the resected colonic tissues in 10 patients and by a positive specific serological test in one patient. In those who presented with diarrhoea laboratory tests included stool examination and culture, serological tests for enteric fever and blood culture. All 11 patients underwent exploratory laparotomy and received intensive postoperative supportive treatment including parenteral antibiotics (penicillin or chloramphenicol with gentamicin or kanamycin), fluid and electrolyte replacement and blood transfusion when indicated. When the diagnosis of amoebiasis was made the patients were given either dehydroemetine or metronidazole or both.

Results

The clinical features are shown in *Table I*. The patients in this series belonged to the low socioeconomic groups. One patient (*Case* 10) had a previous history of treated amoebic dysentery and remained asymptomatic until the present attack. All except 2 patients appeared to be in good health previously. Of the 2 debilitated patients one was a young heroin addict who contracted the disease while in prison (*Case* 4). This patient had had diarrhoea for 4 months and may have been malnourished before the colitis. The other ill patient (*Case* 11) was an elderly man with congestive cardiac failure.

In all but *Case* 4, already referred to, there was only a short history of diarrhoea, varying from 2 days to 3 weeks. In one patient (*Case* 3), whose disease was confined to the right colon, there was no history of diarrhoea. The onset of diarrhoea was usually abrupt with 5–15 stools per day and was associated with toxaemia and abdominal tenderness. In some patients (*Cases* 6 and 7) the diarrhoea was watery and explosive initially, simulating acute bacillary dysentery. Many patients (*Cases* 1, 2, 6, 7 and 9) denied the presence of blood in the stools but red and white blood cells were often found on microscopic examination. In most cases mucus was present and mixed with a small amount of loose stool with each bowel action. As the disease progressed the toxaemia and the frequency of the diarrhoea increased. Eventually the diarrhoea consisted of continuous passage of copious white glairy mucus exudate mixed with occasional necrotic casts of mucosa.

In spite of very severe colitis, amoebae could not be demonstrated on initial microscopic examinations of the stools in 7 of 8 patients. Subsequent stool examinations revealed numerous amoebae in 2 of these 7 patients. Hence preoperative confirmation of amoebic colitis was possible on the basis of stool examination in 3 patients only (*Cases* 1, 4 and 5); in only 2 (*Cases* 4 and 5) was there sufficient time to commence anti-amoebic treatment. One patient (*Case* 11) received preoperative anti-amoebic therapy for suspected giardiasis.

The progress to colonic gangrene and peritonitis was rapid, varying from 4 days to 3 weeks in most patients and after a chronic course of 4 months in only 1 patient (*Case* 4). In most patients there was no dramatic turning point to indicate the onset of gangrene of the colon. The clinical picture was that of gradual deterioration as indicated by the worsening of toxaemia, abdominal distension, tenderness and diarrhoea. Only when peritonitis had become fully established was gangrene of the colon with rupture recognized. A delay in recognition of colonic gangrene of up to 2 days occurred in 8 patients, up to 3 days in 2 patients (*Cases* 4 and 6) and 4 days in 1 patient (*Case* 11).

Operative findings and management

The inflamed and extremely friable colon was usually found wrapped in omentum and adherent to the

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Table I: FEATURES OF 11 CASES OF FULMINATING COLITIS

No.	Age/Sex (yr)	Duration before adm. (d)	*E. hist.* in stool	Preop. diagnosis	Adm. to op. (d)	Op. to death (d)	Extent of necrosis	Procedure	Result
1	60/F	20	+	Typhoid	4	—	Entire colon	Total colectomy, ileostomy and closure of rectal stump	Surv.
2	29/F	2	—	Bacillary dysentery	2	4	Entire colon	Caecostomy, drainage	Died
3	71/M	10	—	Appendix abscess	3	14	Entire colon except distal sigmoid	Subtotal colectomy, ileostomy and mucous fistula	Died
4	44/M	120	+	Amoebic colitis	4	14	Entire colorectum	Panproctocolectomy	Died
5	39/F	10	+	Amoebic colitis	6	—	Entire colon	Total colectomy, ileostomy and mucous fistula	Surv.
6	3/M	6	—	Bacillary dysentery	1. 7 2. 10	14	Caecum to descending colon	1. Caecostomy 2. Drainage	Died
7	85/M	14	—	Bacillary dysentery	2	5	Entire colon	Total colectomy, ileostomy and closure of rectal stump	Died
8	58/F	10	—	Peritonitis	0	—	Caecum to mid-transverse colon	Right colectomy	Surv.
9	50/F	5	—	1. Appendix abscess 2. Amoebic colitis	1. 4 2. 8	—	Caecum to mid-transverse colon	1. Caecostomy, ileo-transverse bypass 2. Right colectomy	Surv.
10	71/M	7	—	Amoebic colitis	0	—	Entire colon except distal sigmoid	Subtotal colectomy, ileostomy and mucous fistula	Surv.
11	60/M	14	—	Giardiasis	1. 5 2. 15 3. 17	21	Entire colon	1. Drainage 2. Ileostomy 3. Total colectomy	Died

Adm., admission; op., operation; *E. hist.*, *Entamoeba histolytica*; surv., survived.

inflamed parietal peritoneum. There were areas of full-thickness colliquative necrosis and areas with relatively normal serosa concealing complete mucosal necrosis. Perforations were usually multiple and widely distributed. Many perforations were partially concealed in the inflamed omental envelope and became evident as soon as the colon was touched. In more severe cases long necrotic segments of the colon had completely disintegrated with free spillage of content. The extent of colonic involvement was as shown in *Table I*. Conservative surgery, i.e. drainage with external faecal diversion or internal bypass, was performed in 3 patients (*Cases* 2, 6 and 9) with disastrous consequences. It resulted in rapid deterioration due to spreading colonic necrosis in spite of specific anti-amoebic treatment. One of these patients (*Case* 2) died within 4 days of the operation from severe toxaemia, 2 patients required re-exploration because of peritonitis and only 1 patient (*Case* 9) survived after a colonic resection. Conservative surgery was used as a temporary procedure in 1 patient (*Case* 11) in the hope that the patient might improve sufficiently to allow colonic resection later. There was no improvement and the patient died after colectomy.

Resection of the diseased colon with external faecal diversion and abdominal drainage was performed in 7 patients and 4 survived.

Mortality

Six patients in this series died, giving an overall mortality of 55 per cent. Early postoperative deaths were due to shock and toxaemia while late deaths were due to sepsis. The mortality rate was 75 per cent among those who had conservative surgery such as diversion and drainage as the primary procedure and 43 per cent for those who had resection with exteriorization as the primary procedure. The mortality was related to the extent of colonic necrosis. When the disease was confined to the area proximal to the mid-transverse colon the mortality was 33 per cent compared with 57 per cent with more distal colonic involvement and 100 per cent with entire colorectal involvement. Mortality was also related to the preoperative condition of the patients. Among those with a poor preoperative state, as characterized by persistent shock (systolic blood pressure below 100 mmHg), associated cardiopulmonary insufficiency, electrolyte imbalance and hypoproteinaemia with generalized oedema, the mortality was 80 per cent compared with 33 per cent in those in a better preoperative condition. Delay of more than 48 h in the diagnosis of colonic necrosis and peritonitis also resulted in a mortality of 67 per cent, twice as high as in those with an earlier diagnosis (38 per cent).

Discussion

Fulminating amoebic colitis has been observed in debilitated subjects who are suffering from malnutrition, chronic illnesses and intestinal infections (Adams and Maegraith, 1960). In an area where amoebiasis is endemic, infestation with various intestinal parasites is also rife. The role of these parasites in the pathogenesis of fulminating amoebic colitis is not known. Their association in many of our cases, together with the low socioeconomic background of the patients, is indicative of the poor hygiene and low standard of health of these people. Similar predisposing factors have been observed by others (Palaez et al., 1966).

The diagnosis of amoebic colitis normally rests on the typical history of bloody mucous diarrhoea, proctoscopic or sigmoidoscopic observation of typical amoebic ulcers and, particularly, the demonstration of *E. histolytica* in the stools and mucus. In fulminating amoebic colitis the diagnosis is difficult because of its unusual presentation. The disease runs a fulminating course in most patients, with diarrhoea of varying severity. The diagnosis on clinical history is relatively easy only in the rare event of the disease superimposing upon the chronic form of amoebic colitis. Sigmoidoscopy is difficult because of the almost continuous passage of mucus and because the friability of the colon makes it hazardous. When performed gently and skilfully without air insufflation, sigmoidoscopy may provide a diagnosis in a limited number of patients with rectal or sigmoid involvement. The curious periodic absence of amoebae in the stools further compounds the diagnostic difficulty and much valuable time is lost in pursuing alternative diagnoses such as bacillary dysentery, typhoid or even idiopathic ulcerative colitis, which is very rare in Thailand. By the time amoebiasis is confirmed it is often too late to commence effective anti-amoebic therapy. We feel that in an area where amoebiasis is endemic a trial of anti-amoebic therapy is worth while in patients with severe, undiagnosed colitis. In such instances the diagnosis must depend first upon the therapeutic response and later on the result of specific serological tests. Prompt anti-amoebic therapy may arrest the progress towards irreversible colonic necrosis in some patients and in others may improve the prognosis should surgery become necessary. The cardiac toxicity of emetine makes it unsuitable in many patients who are already hypotensive from toxaemia; metronidazole is much safer and equally effective.

The detection of colonic necrosis without perforation is difficult in fulminating amoebic colitis because its development is insidious and is usually masked by severe pre-existing local signs and toxaemia. Mucous diarrhoea often continues in the presence of colonic necrosis and peritonitis. By the time perforation is recognized from the X-ray evidence of free air under the diaphragm the patients are usually very ill from toxaemia, making operation hazardous. Clearly every effort must be made to detect the stage of irreversible colonic necrosis and to operate before the patient's condition becomes precarious. This requires an awareness of the diagnosis and vigilant monitoring of the vital signs, abdominal girth, tenderness, severity of diarrhoea and frequent abdominal X-rays to detect dilated featureless colon (toxic megacolon). False optimism on the confirmation of the amoebic nature of the colitis must be resisted. Severe amoebic colitis may require operation at any stage and anti-amoebic drugs cannot prevent a necrotic colon from sloughing even if all amoebae have been eradicated (Stein and Bank, 1970; Mukerjee and Nigam, 1975). We agree with Stein and Bank (1970) that persistent diarrhoea, abdominal tenderness and severe toxaemia, despite adequate anti-amoebic therapy, are indicative of severe colonic necrosis and the need for operation.

Our results suggest that there is no place for conservative surgery, particularly in undiagnosed or untreated patients. It has long been known that diversion, or diversion alone, seems to accentuate the sloughing of the necrotic colon (Manson-Bahr, 1939). The best operative treatment is primary resection of the diseased bowel with exteriorization of the ends in all patients who are fit for laparotomy.

In the past fulminating amoebic colitis always carried a mortality approaching 100 per cent, whatever the form of operative treatment (Hawe, 1945; Rives et al., 1955; Palaez et al., 1966; Chen et al., 1971; Sharma et al., 1975). This was due to the poor preoperative state as a result of delay or inadequate surgical treatment or both. The overall mortality in this series is 55 per cent and indicates that fulminating amoebic colitis is not inevitably fatal. It is our contention that we can reduce the mortality further by employing a high degree of suspicion, prompt anti-amoebic therapy, careful clinical evaluation and, if there is not rapid improvement, adequate resectional surgery.

References

ADAMS A. R. D. and MAEGRAITH B. G. (1960) *Clinical Topical Diseases*, 2nd ed. Oxford, Blackwell Scientific, p. 8.

CHEN W. J., CHEN K. M. and LIN M. (1971) Colon perforation in amoebiasis. *Arch. Surg.* **103**, 676–680.

HAWE P. (1945) The surgical aspect of intestinal amoebiasis. *Surg. Gynecol. Obstet.* **81**, 387–404.

MANSON-BAHR P. H. (1939) *The Dysenteric Disorders*. London, Cassell.

MUKERJEE S. and NIGAM N. (1975) Amoebic perforation of the colon. *Am. J. Proct.* **26**, 57–63.

PALAEZ M., VILLAZON A. and ZARABOSO R. S. (1966) Amoebic perforation of the colon. *Dis. Colon Rectum* **9**, 356–362.

RIVES J. D., HEIBNER W. C. and POWELL J. L. (1955) The surgical complications of amoebiasis of the colon. *Surg. Clin. North Am.* **35**, 1421–1426.

SHARMA B. D., CHOORAMANI S. and AGARWAL A. K. (1975) Acute amoebic necrosis of bowel. *Am. J. Proct.* **26**, 57–62.

STEIN D. and BANK S. (1970) Surgery in amoebic colitis. *Gut* **11**, 941–946.

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Bleeding duodenal ulcer: reduction in mortality with a planned approach

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SUMMARY

In a 6-year prospective study from 1972 to 1978 266 patients were admitted to a haematemesis and melaena unit with bleeding duodenal ulcer. There were 13 deaths, a mortality of 5 per cent. A comparison between the three consecutive 2-year periods of study showed an initial mortality of 6 per cent for the first 4 years falling to 2 per cent for the 93 admissions during the final 2 years of experience. Of the 120 patients treated surgically, 10 died in hospital, giving an operative mortality of 8 per cent. The trend in operative mortality was from 13 per cent for the initial 2-year period to 8 per cent for the second period and to 3 per cent for the final 2 years. The operative rate was consecutively 45, 50 and 34 per cent. There was 1 death in conservatively treated patients during each 2-year period of study. Three types of operation were performed: vagotomy, pyloroplasty and oversewing of the ulcer; Polya gastrectomy; and vagotomy and antrectomy. There was no difference in morbidity and mortality between these operations. At a mean follow-up of 3·1 years, 90 per cent of the patients had a good result from their operation. It is concluded that a prospective system of management with an active policy of early endoscopy, surgery and regular audit reduces the mortality from bleeding duodenal ulcer.

BLEEDING chronic duodenal ulcer is the commonest cause of haematemesis and melaena. Retrospective studies have shown that this disease accounts for more than 30 per cent of admissions with upper gastrointestinal haemorrhage and that bleeding duodenal ulcer is a significant cause of death in hospital practice, with a mortality of 5–7 per cent (Schiller et al., 1970; Hardy, 1974). In addition, Schiller et al. (1970) showed that over a 15-year period their mortality rate remained constant. These authors noted an emergency operative rate of 29 per cent, and concluded that to improve results emergency surgery should be performed more frequently and that vagotomy with drainage is the operation of choice.

At our hospital retrospective analysis of the period from 1951 to 1970 showed an unacceptably high mortality of about 12 per cent for bleeding duodenal ulcer. This finding prompted the establishment of a haematemesis and melaena unit in 1972. Patients were managed according to a defined protocol depending on the cause of bleeding. All patients presenting to the hospital with this problem were admitted to the unit. Thus, this unit managed the complete sample of patients with bleeding duodenal ulcer presenting from an Australian urban setting. Prospective analysis of these patients is reported in an attempt to study whether such a unit influences the outcome of patients with bleeding chronic duodenal ulcer.

Patients and methods

There were 894 admissions to the unit over the 6 years of prospective study from 1972 to 1978. The total number of admissions due to bleeding duodenal ulcer was 282. All patients were admitted to a designated area of the hospital under the care of a gastroenterologist, surgeon and gastroenterology registrar. The policy of management specified immediate resuscitation and endoscopy within 12 h of admission. The indication for blood transfusion was shock and/or a haemoglobin of less than 10 g/dl. Patients were endoscoped with the forward-viewing Olympus or ACMI instruments. During the first year of the study all patients had a subsequent barium meal examination, but later this was only performed in those patients unsuitable for endoscopy or where the diagnosis remained in doubt.

In chronic duodenal ulcer an active policy of surgical management was pursued. This approach was substantiated by a review of results at 3 years (Sereda et al., 1977) which confirmed that patients over 50 years of age and shocked were the most likely to die. Surgery was performed in such patients after resuscitation, and in those with recurrent or continued bleeding requiring more than 5 units of blood. Four surgeons were involved and the policy of the unit was for those surgeons to perform their preferred operation. The operations performed were Polya partial gastrectomy, truncal vagotomy, pyloroplasty and oversewing of the ulcer and truncal vagotomy and antrectomy with a Polya anastomosis.

Exhibition of the protocol and 6 monthly reports within the hospital were considered an important part of the method. Every patient admitted was discussed at weekly gastroenterology meetings.

Results

Overall results

There were 282 admissions to the unit with bleeding duodenal ulcer. This group comprised 266 patients (156 females and 110 males) of a mean age (± s.d.) of 54·4 ± 17 years. Sixteen patients were admitted on two occasions (89 per cent). Emergency surgery was performed on 120 patients (43 per cent), whilst for 162 admissions conservative treatment was followed. Of the 16 patients readmitted on a second occasion, 6 underwent emergency surgery whilst 10 were again treated conservatively, either because of associated disease (cancer, severe cardiac or respiratory disease) or because they refused surgery (*Table I*).

There were 13 deaths during the 6-year period (4·5 per cent). Ten occurred in patients who underwent emergency surgery whilst 3 patients died (1 following endoscopic perforation) in the group that was treated medically. The haemodynamic data from these patients revealed that 121 (43 per cent) received more than 5 units of blood, 164 (58 per cent) had a haemoglobin of 10 g/dl or less on admission and 85 (30 per cent) were shocked on admission (*Table II*).

There were associated lesions in the upper gastrointestinal tract of 54 patients at endoscopy. These were not the source of major bleeding. This included 15 patients with acute gastric ulceration; 4 with small

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Table I: DATA FOR 282 ADMISSIONS WITH BLEEDING DUODENAL ULCER OVER 6 YEARS

	No.	Medical therapy	Emergency surgery
Total admissions	282	162	122
First admissions	266	152	114
Readmissions	16	10	6

Table II: OVERALL RESULTS FOR BLEEDING DUODENAL ULCER

Admissions	282
Patients	266
Endoscopic diagnosis	260
Deaths	13
Operative deaths	10
>5 units blood	121
Hb 10 g/dl or less	164
Shock	85

Table III: TREND IN PROSPECTIVE CLINICAL EXPERIENCE OVER 6 YEARS

	1972–4	1974–6	1976–8
Number of admissions	88	101	93
Deaths	6	5	2
Operations	40	50	32
Operative deaths	5	4	1
Endoscopic diagnosis	64	97	91
>5 units blood	48	42	31
Hb 10 g/dl or less	45	55	61
Shock	23	37	25

Table IV: RESULTS OF MEDICAL MANAGEMENT AND FOLLOW-UP

Total admissions	162
Rebleeds	16
Total patients	152
Past bleed	53
Inpatient deaths	3
Follow-up deaths	21
Total follow-up	113
Elective operations	25
Emergency operation at rebleed	6
Proved recent ulcers	15

Table V: RESULTS OF SURGICAL MANAGEMENT AND FOLLOW-UP

	Polya	V+P*	V+A	O	Total
No.	58	44	19	1	122†
Operative death	5	3	1	1	10
Late death	3	3	—	—	6
Lost to follow-up	5	1	1	—	7
Visick I+II	39	33	17	—	89
Visick III+IV	6	4	—	—	10
Recurrent ulcer	2	1	—	—	3

V+P, Vagotomy and pyloroplasty; V+A, vagotomy and antrectomy; O, oversew.
* 33 truncal and 11 selective vagotomy.
† 120 patients.

varices; 6 with chronic benign gastric ulcer; 5 with Mallory–Weiss tear; 14 with oesophagitis; 9 with hiatus hernia; and in 1 patient there was also a pyloric channel ulcer.

Trend in clinical experience

In order to evaluate trends, comparison was made between the three consecutive 2-year periods of study (*Table III*). During 1972–4 there were 88 admissions with duodenal ulcer and 6 deaths (7 per cent); 1974–6, 101 admissions and 5 deaths (5 per cent); 1976–8, 93 admissions and 2 deaths (2 per cent). The operative mortality was 5 of 40 operations (13 per cent) for the first 2 years, 4 of 50 operations (8 per cent) for the second 2-year period and 1 of 32 operations (3 per cent) for 1976–8. The operative rate has varied from 45 per cent to 50 per cent to 34 per cent in each 2-year period. In the medically treated patients there was 1 death in each 2-year period. There was no change in the incidence of shock on admission. The endoscopic diagnostic rate rose from 73 per cent in 1972–4 to 97 per cent for 1974–6 to 98 per cent for 1976–8.

Results of medical management and follow-up

A total of 152 patients was admitted and treated medically, 16 of these were readmitted and 10 were again treated conservatively (*Table IV*). Thus, for 162 admissions medical treatment was followed. The mean (± s.d.) age of this group of patients was 54 ± 17 years. In 53 of these patients (34 per cent) there was a past history of upper gastrointestinal bleeding.

Three patients died in hospital. Follow-up has revealed that a further 21 patients have died from 3 months to 5 years after admission. The cause of death was from diseases unrelated to duodenal ulcer, except in one patient who died from massive gastrointestinal bleeding at another hospital. There were 16 patients lost to follow-up, giving a follow-up rate of 89 per cent for a mean period of 2·9 years. Twenty-five patients subsequently underwent elective surgery for duodenal ulcer, usually for symptoms not controlled by medical management.

Results of surgical management and follow-up

One hundred and twenty patients were treated by emergency operation (43 per cent) (*Table V*). Six of these patients had previously been admitted to the unit. The mean (± s.d.) age of these patients was 57 ± 15 years. There were 10 deaths, giving an operative mortality of 8 per cent. Three varieties of procedure were performed with no difference in mortality for each procedure. Six patients died more than 3 months after discharge; 4 deaths were due to diseases unrelated to duodenal ulcer and in 2 cases the cause of death was unknown. Seven patients were lost to follow-up giving a follow-up rate of 94 per cent.

These patients were followed for a mean of 3·1 years and clinical results were assessed according to Visick criteria as modified by Goligher et al. (1978). Of the 45 patients treated by Polya gastrectomy 39 were Visick grade I or II (81 per cent). There were two proved recurrent ulcers in this group. Of the 37 patients followed up after truncal vagotomy and pyloroplasty 33 were Visick grade I or II (75 per cent), and there was 1 proved recurrent ulcer. All 17 patients followed up after truncal vagotomy and antrectomy were Visick grade I or II at completion of this follow-up study.

Discussion

In this prospective study the overall mortality was 5 per cent, which compares favourably with available complete retrospective reports from Britain (Schiller et al., 1970) and North America (Himal et al., 1974). Most studies have the disadvantage of being retrospective and of taking only an incomplete sample of patients presenting to individual hospitals. This

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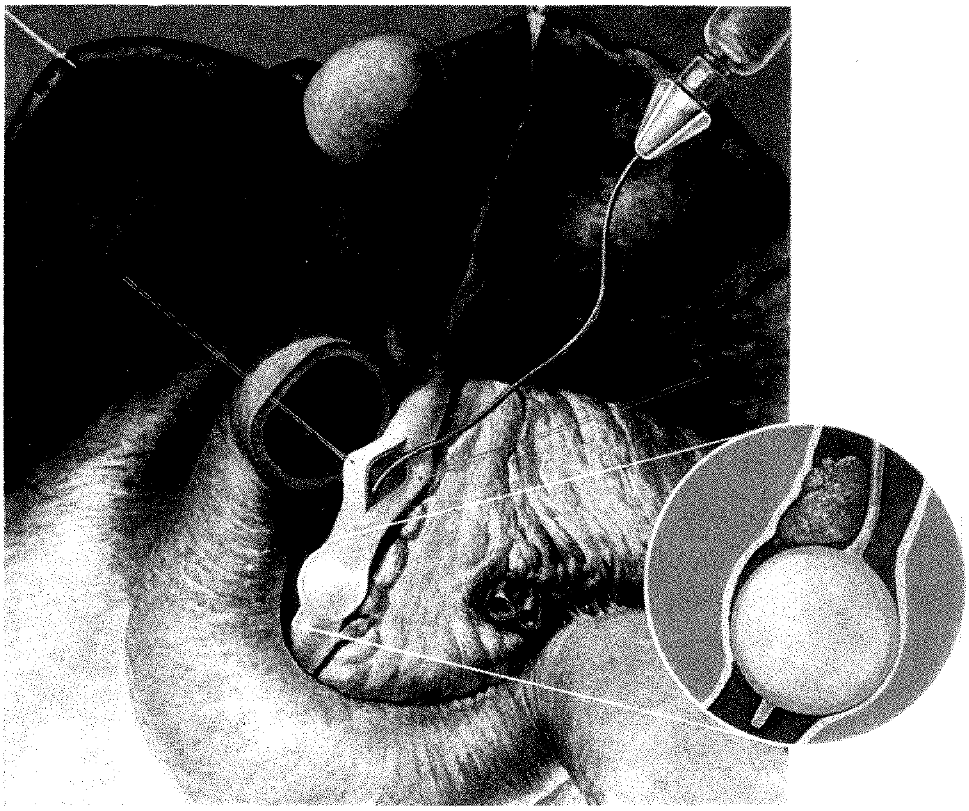

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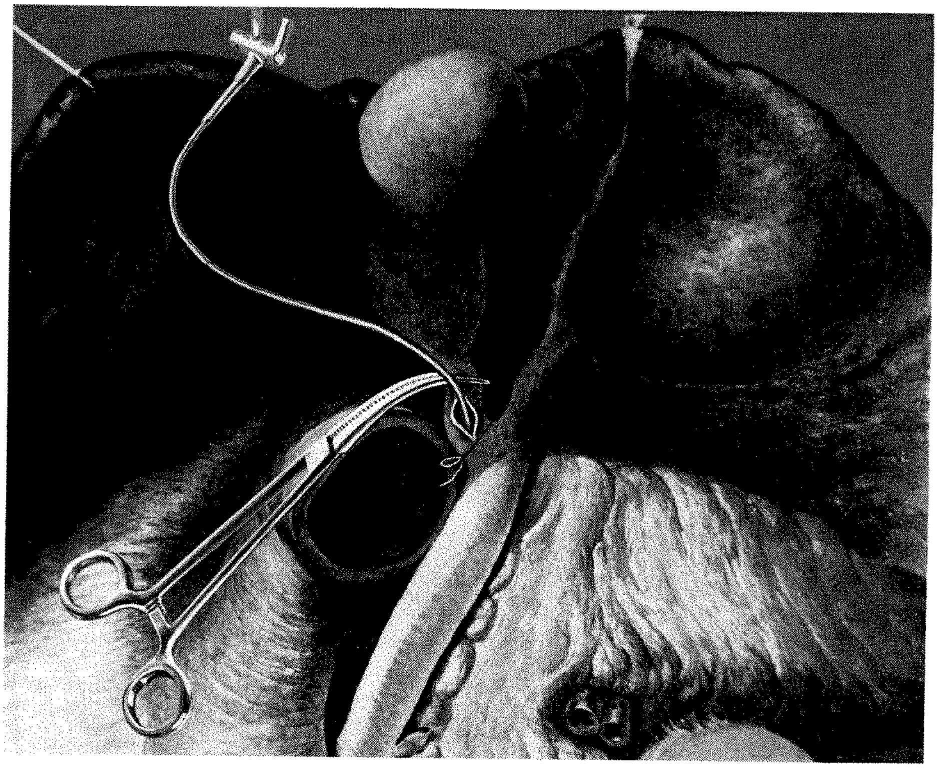

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prospective study suggests that with a planned approach to the problem, mortality can be reduced and supports the concept of early endoscopy and an active surgical approach. Early surgery, particularly in patients over 50 years of age, is supported by the experience of Jones et al. (1973) in Aberdeen, who noted a significant relationship between mortality and further haemorrhage in hospital in patients of over 60 years of age or with coincidental disease.

During the three 2-year periods the mortality trend was from an initial mortality of 6 per cent during the first 4 years to 2 per cent in the final 2 years. During the last year of the study there were no deaths in 45 admissions, 16 of whom underwent surgery. In a retrospective study at Prince Henry's Hospital, the surgical mortality for bleeding duodenal ulcer was 24 per cent for 1951–60 and 17 per cent for 1961–70 (Hunt et al., 1978). Before the unit was established patients were usually managed in medical units, diagnosis was not made early and surgical consultation was often late. Correction of these factors by admission to a specialist unit, early endoscopic diagnosis and a combined medical/surgical approach has possibly been responsible for the decreased mortality. There must be an occasional patient with advanced disease (cancer, cardiac or respiratory disease) or extreme age in whom no treatment is desirable. This accounted for 2 of 3 deaths in the medically treated group. The natural history of the medically treated patient is of interest. In 35 per cent there was a past history of upper gastrointestinal bleeding. This supports the contention of Hallenbeck (1970) that recurrent bleeding is common.

The surgical mortality was 8 per cent. This compares favourably with the best retrospective results from Britain and North America (Schiller et al., 1970; Himal et al., 1974), these series reporting mortalities of 7–9 per cent for urgent surgery in bleeding duodenal ulcer. The surgical mortality at Prince Henry's Hospital showed an initial mortality of 13 per cent during the first 2 years falling to 8 per cent for the second 2 years to a final 2-year surgical mortality of 3 per cent. The latter result compares with the best result of 2 per cent reported from Sydney (Bambach et al., 1976). A prospective study from Montreal (Himal et al., 1978) has also shown a fall in mortality for bleeding duodenal ulcer to 2 per cent.

The reduced mortality associated with the more conservative operation (Carruthers et al., 1967; Schiller et al., 1970), i.e. vagotomy and pyloroplasty, was not seen in this study—the three operations having an operation mortality of 5–8·5 per cent. While individual surgeons in the unit had a preference for a particular operation, in practice, each surgeon performed a variety of operations depending upon the circumstances. Partial gastrectomy of the Polya type was performed when vagotomy might have been difficult, such as when varices were present, or when there was marked obesity or an enlarged left lobe of the liver. Also, some surgeons chose partial gastrectomy instead of pyloroplasty when there were very large circumferential oedematous duodenal ulcers. Thus, partial gastrectomy was performed in some poor risk patients though there is little doubt that vagotomy, pyloroplasty and oversewing is the most effective, expeditious operation to be generally recommended, especially in the aged. Rebleeding was uncommon and rarely severe. In only one case having undergone vagotomy and pyloroplasty was reoperation necessary for rebleeding. This was early in the series and it is clear that careful oversewing of the ulcer with non-absorbable sutures is essential to prevent this complication. Follow-up of patients though incomplete (94 per cent) and early (mean, 3 years) suggests that sequelae were uncommon, which is in agreement with the results of Goligher et al. (1978).

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References

BAMBACH C. P., COUPLAND G. A. E. and CUMBERLAND V. H. (1976) Haematemesis and melaena—surgical management. *Aust. NZ J. Surg.* **46**, 107–111.

CARRUTHERS R. K., GILES G. R., CLARK C. G. et al. (1967) Conservative surgery for bleeding peptic ulcer. *Br. Med. J.* **1**, 80–100.

GOLIGHER J. C., HILL G. L., KENNY T. E. et al. (1978) Proximal gastric vagotomy without drainage for duodenal ulcer. *Br. J. Surg.* **65**, 145–151.

HALLENBECK G. A. (1970) Elective surgery for treatment of haemorrhage from duodenal ulcer. *Gastroenterology* **59**, 784–789.

HARDY K. J. (1974) Haematemesis and melaena: a clinical study of 251 hospital admissions. *Aust. NZ J. Surg.* **44**, 388–393.

HIMAL H. S., PERRAULT C. and MZABI R. (1978) Upper gastrointestinal haemorrhage: aggressive management decreases mortality. *Surgery* **64**, 448–452.

HIMAL H. S., WATSON W. W., JONES C. W. et al. (1974) The management of upper gastrointestinal haemorrhage. *Ann. Surg.* **179**, 489–493.

HUNT P. S., ELLIOTT B., FREIDIN J. et al. (1978) Mortality trends in the surgical management of chronic peptic ulceration. *Aust. NZ J. Surg.* **48**, 147–151.

JONES P. E., JOHNSTON S. J., MCEWAN A. B. et al. (1973) Further haemorrhage after admission to hospital for gastrointestinal haemorrhage. *Br. Med. J.* **3**, 660–664.

SCHILLER K. F. R., TRUELOVE S. C. and WILLIAMS D. G. (1970) Haematemesis and melaena with special reference to factors influencing outcome. *Br. Med. J.* **2**, 7–14.

SEREDA S., LAMONT I. and HUNT P. (1977) The experience of a haematemesis and melaena unit. *Med. J. Aust.* **1**, 362–366.

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Anti-Xa factor as a predictor of postoperative deep vein thrombosis in general surgery

IAIN G. GUNN*

SUMMARY
This study was stimulated by a recent report linking a low preoperative level of an endogenous coagulation inhibitor (anti-Xa factor) with an increased incidence of postoperative deep venous thrombosis (DVT) (Stamatakis et al., 1977).

Preoperative and postoperative levels of anti-Xa were measured and correlated with the postoperative incidence of deep venous thrombosis assessed by the ^{125}I fibrinogen uptake test to determine whether a high risk group could be isolated and a suitable regimen of prophylaxis introduced.

In this study of 22 surgical patients the postoperative DVT rate was 41 per cent. However, preoperative measurements of anti-Xa activity failed to show any statistically significant difference between those patients with DVT and the non-DVT group. The findings do not support the use of anti-Xa levels as a preoperative predictor of postoperative DVT in the individual.

ANTI-XA factor is thought to be important in the pathogenesis of DVT as an endogenous, homeostatic neutralizer of factor Xa which itself generates relatively large quantities of thrombin from thromboplastin. Thus a patient with a low preoperative level of anti-Xa activity may be unable to maintain equilibrium in the face of considerable quantities of factor Xa generated by surgical trauma. This would result in a hypercoaguable state producing an increased incidence of postoperative DVT. This study aimed to assess this connection between anti-Xa levels and the occurrence of DVT.

Patients and methods

A total of 22 patients from the general surgical wards of the Southern General Hospital, Glasgow, were studied. All these patients underwent elective procedures involving either laparotomy or thoracotomy. Their mean age was 58 years, with a range of 34 to 80 years. No special prophylactic measures other than early ambulation were taken to prevent postoperative thrombosis.

Plasma samples for anti-Xa estimations were drawn by venepuncture at least 12 h preoperatively. Further samples were taken during the operative procedure and 24 h postoperatively. Anti-Xa levels were assessed by the technique of Yin and Wessler (1970) which is specific in estimating the anti-Xa activity of plasma.

Assessment of patients for postoperative DVT employed the ^{125}I fibrinogen uptake test, the accuracy of which has already been established (Flanc et al., 1968; Kakkar and Flanc, 1968). One hundred μCi of ^{125}I fibrinogen were administered intravenously immediately after the preoperative anti-Xa sample had been withdrawn. Two hours later preoperative reference scans of both legs in seven positions from the ankle to the level of the adductor canal were performed. Diagnostic scans were carried out on postoperative days 1, 3, 5, 7 and 9 with daily scans of any leg showing significantly increased uptakes.

Using this technique 9 out of the 22 patients (41 per cent) were considered to have developed DVT and the preoperative anti-Xa levels of these patients and of the non-DVT group are shown (*Fig.* 1).

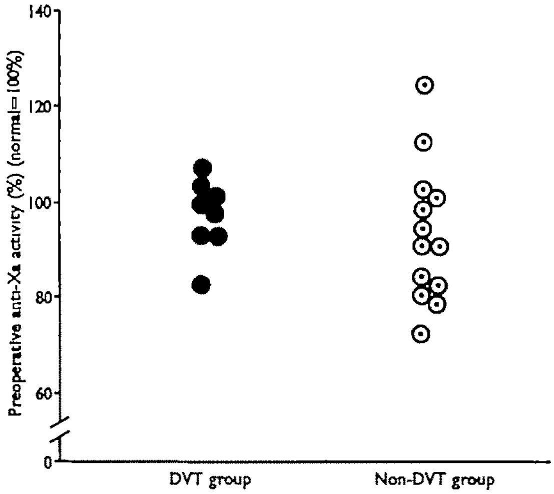

Fig. 1. Preoperative anti-Xa levels in 22 patients.

Conclusion

In this study no correlation is evident between preoperative low anti-Xa levels and postoperative DVT: in fact, the mean preoperative anti-Xa levels are higher (99 per cent) in the DVT group than in the non-DVT group (96 per cent). Six patients had a low preoperative anti-Xa level of less than 90 per cent but only one of these developed postoperative thrombosis. Similarly, the anti-Xa levels estimated intra- and postoperatively failed to show any statistically significant differences between the DVT and non-DVT groups.

Although anti-Xa may yet prove to be an important factor in our understanding of postoperative DVT, this study indicates that a preoperative assessment of the activity of this coagulation inhibitor cannot accurately predict the risk of postoperative DVT in an individual patient and thus is not a useful measurement on which to base anti-thrombosis prophylaxis.

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References

FLANC C., KAKKAR V. V. and CLARKE M. B. (1968) The detection of venous thrombosis of the legs using ^{125}I-labelled fibrinogen. *Br. J. Surg.* **55**, 742–747.
KAKKAR V. V. and FLANC C. (1968) The role of phlebography in deep venous thrombosis. *Br. J. Surg.* **55**, 384.
STAMATAKIS J. D., LAWRENCE D. and KAKKAR V. V. (1977) Surgery, venous thrombosis and anti-Xa. *Br. J. Surg.* **64**, 709–711.
YIN P. T. and WESSLER S. (1970) Heparin accelerated inhibition of activated factor X by a natural plasma inhibitor. *Biochem. Biophys. Acta* **201**, 387–390.

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The fibrinolytic activity of the vein following venous stasis

ANDREW V. O. WU AND AVERIL MANSFIELD*

SUMMARY

This animal study investigated the fibrinolytic activity in the vein wall of the pig following venous stasis, which was induced artificially using an intermittently inflated pneumatic cuff. The method used to measure the fibrinolytic activity was modified from Todd's original technique. The area of lysis and the area of the vein wall were measured and expressed as a ratio, called the fibrinolytic index. After 3 h of intermittent venous stasis the fibrinolytic index was reduced by 68 per cent, significantly lower than the control group.

The reduction of the fibrinolytic index by venous stasis could play an important part in the development of deep vein thrombosis.

PERMIN (1947) found that areas of lysis occurred when pieces of tissue were placed on a fibrin clot and incubated. Todd (1958) used a histochemical method to confirm and locate the presence of fibrinolytic activity in the vein wall. Pandolfi et al. (1968) modified this method by grading the areas of lysis and estimated the level of fibrinolytic activity in the veins of volunteers and patients.

We present here a quantitative method, also based on Todd's original technique, to measure the fibrinolytic activity in the vein wall following artificially induced venous stasis.

Materials and methods

Our experimental animal was the pig, each weighing 30–35 kg. Anaesthesia was induced and maintained with fluothane/nitrous oxide/oxygen and with endotracheal intubation.

We used 2 animals for the study of pressure and flow effect of the pneumatic cuff, which was 5 cm wide and was placed around the hind leg of the pig. In one animal the distal part of the femoral vein was exposed and through separate tributaries two fine 21 G plastic catheters were inserted into the deep vein. The tip of one was placed distal to the cuff and the other advanced to the iliac vein. After the catheters were secured the incision was closed and the catheters were connected to the pressure monitor via transducers. The pneumatic cuff was then inflated to a pressure of 225 mmHg for 10 min and this was repeated after 10 min release. Pressure changes in the vein on either side of the cuff were recorded simultaneously during stasis and during release. In the second animal venograms were performed through a peripheral vein to visualize the deep vessels during stasis. Following this the femoral vein was exposed in an attempt to measure the venous flow during stasis. This was unsuccessful. No data could be obtained because the easily collapsible vein made proper contact with the electromagnetic probe technically impossible.

We then studied two groups of pigs. In the stasis group each of the 5 animals had the leg cuff intermittently inflated to the same pressure as before for 20 min and then released for 10 min; the cycle was repeated for a total period of 3 h. In the control group of 5 animals no pneumatic cuff was applied but each animal was anaesthetized for 3 h. From each of these animals a series of biopsies was obtained from the saphenous vein, distal to the cuff, before and at 20, 90 and 180 min after the onset of stasis. Commencing distally, segments of the vein between two tributaries were successively removed at the set time so that the flow of blood in the more proximal part of the vein was maintained and remained in communication with the deep veins. Each vein sample, measuring 5–8 mm in length, was gently rinsed in buffered saline to remove the blood within its lumen. It was placed on a small block of supporting tissue (boiled liver) and was immediately frozen in isopentane cooled by carbon dioxide ice. The sample was then stored at −20 °C until used. Using the Cambridge Cryostat each vein sample was sectioned to a thickness of 10 μm. Each of the eight sections obtained from the same vein sample was placed on a 16-mm round glass coverslip which had been thoroughly cleaned to remove all traces of grease. To facilitate handling, four such coverslips were carried on one microscope slide. Using a Pasteur pipette, a thin film of topical thrombin, at a concentration of 20 units/ml, was applied over the vein section. Then, 0·05 ml of a mixture of fibrinogen, plasminogen and phosphate buffer (Pandolfi et al., 1968) was gently spread over the whole area of the coverslip. After 15 min in a moist chamber, at room temperature for the fibrin to consolidate, the plates were placed in a moist incubator at 37 °C. At the end of 1 h the plates were placed in a solution of 10 per cent buffered formalin for 10 min. The plates were then stained with Harris's haematoxylin and then Giemsa stain before being left at room temperature to dry.

On examination under the microscope the lytic areas were clearly seen to be related mainly to the adventitia of the vein. The total area of lysis was measured in mm² with the aid of a counting grid attached to the eyepiece. The area of the vein wall was measured by the product of the length of the intima and the mean thickness of the vein wall. The fibrinolytic index was calculated as a ratio in the following formula:

$$\text{fibrinolytic index} = \frac{\text{area of lysis mm}^2}{\text{area of vein wall mm}^2}.$$

The fibrinolytic index for the vein was the mean obtained from eight separate sections of that vein. In order to detect any contaminating activator substance, as controls, sections of boiled liver were processed in the same way at the same time.

Results

The venogram (*Fig*. 1) shows that there are two large deep veins draining the pig's hind leg, and when the cuff is inflated the more superficial femoral vein is occluded at the level of the cuff, but the other deep vein is only slightly narrowed with no interruption of flow. The pressure curve (*Fig*. 2) shows that when the cuff is inflated the distal venous pressure rises sharply but within 2 min it falls to normal and remains low until the cuff is released when there is another drop in pressure. The second and subsequent cycles show that the pressure spikes are even smaller than the initial one, indicating the presence of venous dilatation and a diversion of the blood flow to the alternative deep drainage system. In the iliac vein the pressure curve has an opposite and much lesser effect. These experiments suggest that the thick fleshy hind quarter of the pig protects the deep veins from complete occlusion by the cuff. There is stasis because the peripheral veins are dilated (*Fig*. 1) but venous hypertension is absent. The range of pressure applied to the cuff to produce the desired stasis effect is wide. It is almost impossible to produce complete vascular occlusion with this method.

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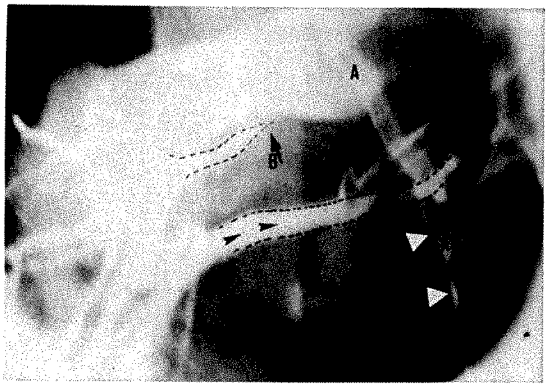

Fig. 1. Venogram taken with the cuff inflated. Arrows point to the direction of blood flow. A, level of cuff; B, occluded superficial femoral vein; C, deep vein slightly narrowed but patent.

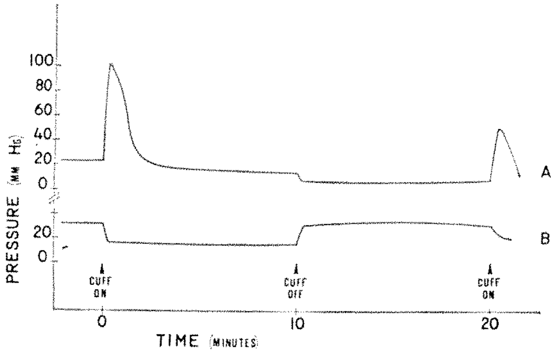

Fig. 2. Time/pressure curve recorded simultaneously from two catheters inserted into the superficial femoral vein. A, pressure distal to the cuff, no persistent venous hypertension; B, pressure proximal to the cuff.

In the control group of animals (*Table I*), where there was no stasis, the fibrinolytic indices of five animals at 0, 20, 90 and 180 min show an even distribution. Statistical analysis, using the Spearman rank test, shows no correlation between the fibrinolytic index and time. In the stasis group (*Table II*), the fibrinolytic index of each of the five animals shows a diminishing trend. The Spearman rank coefficient here shows a significant negative correlation between fibrinolytic index and time. This indicates a progressive reduction in fibrinolytic activity with stasis. *Table III* shows the mean values of fibrinolytic index in the two groups of animals in relation to the time of stasis. Further analysis using the Wilcoxon rank sum test shows that the two groups are significantly different at the 1 per cent level. At the end of 3 h of stasis the fibrinolytic index has been reduced to 31·58 per cent of the initial level.

Discussion

The fibrinolytic activity in the blood has been extensively investigated. However, this activity in the vein wall poses several difficulties for investigators.

1. Clinically, the vein that is readily available for study is often the long saphenous vein, obtained during varicose vein operations. These are abnormal veins and often have abnormal fibrinolytic activity. They cannot be assumed to be representative.

Table I: FIBRINOLYTIC INDEX IN CONTROL ANIMALS

Pig	Time (min) 0	20	90	180
1	12·45	10·06	4·38	6·79
2	10·9	5·18	5·29	4·58
3	15·01	11·25	17·5	9·09
4	14·35	8·07	16·91	9·97
5	18·87	6·49	14·95	12·77

Spearman rank coefficient $r_s = -0{\cdot}31$, n.s.

Table II: FIBRINOLYTIC INDEX IN STASIS ANIMALS

Pig	Time (min) 0	20	90	180
1	10·78	5·22	11·77	3·83
2	18·68	16·94	10·63	2·55
3	8·99	9·09	6·2	5·21
4	7·08	2·67	3·73	3·85
5	5·18	5·67	5·95	1·02

Spearman rank coefficient $r_s = -0{\cdot}57$, $P < 0{\cdot}01$.

Table III: MEAN VALUES IN FIBRINOLYTIC INDEX IN CONTROL AND STASIS ANIMALS

Group	Time (min) 0	20	90	180
Control ($n = 5$)	14·31	8·21	11·8	8·64
Stasis ($n = 5$)	10·14	7·92	7·66	3·20

Wilcoxon rank sum test significant at 1 per cent level.

2. The small veins of the hand and foot are easily accessible and have been studied to a certain extent but one is limited by the small number of biopsies that can be taken and, therefore, changes in fibrinolytic activity cannot be followed.

3. A new method, devised by Johnson, measures the amount of lysis by its radioactivity released from ^{125}I-tagged fibrin clot (Johnson and Mansfield, 1978). Although this method is simple and quantitative, it is not very precise, for the published data revealed a coefficient of variance of 76 per cent. This method also requires a relatively large vein sample, which is not always obtainable.

4. The standard method for the study of tissue fibrinolytic activity is a qualitative histochemical technique developed by Todd (1958). Pandolfi et al. (1968) modified it by grading the lytic areas according to the degree of confluency. This semiquantitative method has been used frequently to study the fibrinolytic activity of the vein in physiological and pathological conditions (Browse, 1977). Since the process of grading is arbitrary and subjective, the precision of this method cannot be evaluated. Differences in data between studies cannot be easily resolved.

The method used in this study takes into account the total fibrinolytic activity contained in the tissue mass of the vein. Our unpublished data show that the fibrinolytic activity of the vein has a linear relationship with the weight of the vein ($r = 0{\cdot}93$, df $= 8$, $P < 0{\cdot}001$). This may mean that a bigger piece of vein contains a larger number of vasa vasoria where the plasminogen activator is thought to originate. The ratio of the area of lysis and that of the vein wall can be accurately measured. The counting of one area has low variability (coefficient of variance = 6 per cent). After estimating the fibrinolytic index of a very large number of sections from the same normal vein, the coefficient of variance for this method is 31 per cent ($\bar{x} = 9{\cdot}5 \pm 2{\cdot}9$, $n = 32$) when the sections are taken randomly, and 18 per cent when consecutive sections are obtained ($\bar{x} = 8{\cdot}7 \pm 1{\cdot}6$, $n = 30$). This suggests that the fibrinolytic activity at one point can be quite different from an adjacent point. We use random sections of vein in order to avoid misinterpreting our results. Todd's method has many variables. We keep the thickness of the fibrin overlying the vein section uniform by spreading a fixed volume of fibrinogen over a constant area. The other possible variable is the thickness of the vein section cut by the cryostat. The precision of this machine cannot be tested easily. Johnson and Mansfield (1978) showed that the rate of release of plasminogen activator varied greatly with the time of incubation. Pandolfi's method measures the concentration of plasminogen activator at specific active points along the vein and does not take into account the number of active points (Pandolfi et al., 1968). A large number of small lytic areas are graded lower than one bigger area. We chose the incubation time to be 1 h: this is short enough to be convenient and long enough for all the small lytic areas to be confluent. This eliminates another variable and facilitates the counting procedure.

Venous stasis is an important aetiological factor in the development of deep vein thrombosis. *In vivo* stasis is difficult to study as there had been a lack of a suitable experimental model. The method employed in our study produces intermittent stasis and offers an acceptable alternative. Our radiological and pressure studies confirm that the observed changes in fibrinolytic activity in the vein wall are not due to high venous pressure which is associated with venous occlusion. However, there is some low pressure dilatation of the distal venous tree due to the inflated cuff. We feel that this dilatation is probably an integral part of the physiopathological process of clinical venous stasis. Bauer (1940) performed venograms on a supine patient in whom deep vein thrombosis had been excluded. By raising the head of the operating table to 15° the deep veins were shown to be markedly distended. There was delay in the clearance of the contrast medium, indicating venous stasis. The cutaneous veins were also widened.

Venous occlusion results in an increase in the fibrinolytic activity in the blood (Clarke et al., 1960), which is thought to be due to a release of an activator substance from the store within the vein wall. Knight and Dawson (1976) used this phenomenon in an attempt to reduce the incidence of deep vein thrombosis following surgery, and Cliffton et al. (1961) used it to treat a case of superficial thrombophlebitis. Only 2 animals in our stasis group showed an initial rise in fibrinolytic index. After 3 h of stasis there is marked reduction in the fibrinolytic index. It appears that the so-called store of fibrinolytic activity is soon depleted. We have repeated the stasis experiment and subjected the endothelium to examination under the scanning electron microscope. The endothelial cells show evidence of damage within minutes of the onset of stasis (Wu, 1979). With prolonged stasis desquamation of endothelial cells occurs, followed by platelet aggregation. Since the endothelial cells contain a high concentration of plasminogen activator, we postulate that at least part of the depletion of fibrinolytic activity following stasis is due to the loss of endothelial cells into the circulation, resulting in a transient rise in fibrinolytic activity in the blood.

Our observation suggests that venous stasis could reduce the fibrinolytic activity in the vein wall by almost 70 per cent at the end of 3 h. This factor may increase the risk of the development of deep vein thrombosis and its hazards.

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References

BAUER G. (1940) Venographic study of thrombo-embolic problems. *Acta Chir. Scand.* **84**, *Suppl.* 61, pp.1–75.

BROWSE N. L. (1977) Blood and vein-wall fibrinolytic activity in health and vascular disease. *Br. Med. J.* **1**, 478–481.

CLARKE R. L., ORANDI A. and CLIFFTON E. E. (1960) Induction of fibrinolysis by venous obstruction. *Angiology* **11**, 367–370.

CLIFFTON E. E., CLARKE R. L. and MURPHY J. (1961) Studies on fibrinolytic activity with venous occlusion; treatment of thrombophlebitis. *Surgery* **50**, 644–650.

JOHNSON R. H. and MANSFIELD A. O. (1978) A new method for the detection of plasminogen activator content of the vein wall. *Acta Haematol.* **60**, 243–249.

KNIGHT M. T. and DAWSON R. (1976) Reduction of the incidence of deep vein thrombosis in the leg by intermittent compression of arms. *Br. J. Surg.* **63**, 668.

PANDOLFI M., ROBERTSON B. and ISACSON S. (1968) The fibrinolytic activity of human veins in the arms and legs. *Thromb. Diath. Haemorrh.* **20**, 247–256.

PERMIN P. M. (1947) Properties of the fibrinokinase-fibrinolysin system. *Nature (Lond.)* **160**, 571–572.

TODD A. S. (1958) Fibrinolysis autograph. *Nature* no. 4607, p. 496.

WU A. V. O. (1979) *J. Cardiovasc. Surg.* (In the press.)

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The incidence of deep vein thrombosis in Hong Kong Chinese after hip surgery for fracture of the proximal femur

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SUMMARY

Fifty-three Hong Kong Chinese patients with fractures of the proximal femur have been studied after hip surgery using functional ascending phlebograms for evaluating deep vein thrombosis. There was an incidence of deep vein thrombosis of 53·1 per cent in the fractured limbs and 14·3 per cent in the uninjured limbs. The majority of thrombi (84·6 per cent) were located in the calf. No clinical or fatal pulmonary embolism was observed.

A NUMBER of clinical reports, ^{125}I-labelled fibrinogen uptake studies and autopsy reviews suggest that there are differences in the incidence of thromboembolism between different geographical regions and different ethnic groups, with low incidences among Asian and African populations (Thomas et al., 1960; Franz et al., 1961; Dodd, 1964; Gore et al., 1964; Horn and Wang, 1964; Srivastava, 1964; Tinckler, 1964; Sevitt, 1965; Sandritter and Felix, 1967; Hwang, 1968; Baker and Houlder, 1973; Baker and Prajapat, 1974; Chumnijarakij, 1974; Cunningham and Yong, 1974; Hassan et al., 1974; Chumnijarakij and Poshyachinda, 1975; Bong and Chow, 1977; Talalak, 1976). However, Joffe (1974) from Cape Town and Colin et al. (1975) from Nairobi reported that European, Coloured, African and Indian patients were at a similar high risk of venous thromboembolism. True geographical and ethnic differences in the incidence of thromboembolism are of importance, because they might shed some light on the pathogenesis of the condition. A study on the incidence of thromboembolism in clinical practice amongst Chinese patients has never been reported. Clinical observations indicated that venous thromboembolism is a rarity even among 'high risk' Chinese patients (Horn and Wang, 1964; Bong and Chow, 1977). In an autopsy review (Hwang, 1968), the incidence of pulmonary embolism among Chinese in Singapore was found to be low. This article reports the use of phlebography to determine the incidence of deep vein thrombosis in a group of Hong Kong Chinese patients after hip surgery for fracture of the proximal femur.

Patients and methods

Fifty-three Hong Kong Chinese patients (19 males, 34 females), aged 40–83 years, with fractures of the proximal femur, were randomly selected for prospective study for deep vein thrombosis. Informed consent to perform the phlebography was given in writing by each patient. There were 19 intracapsular fractures and 34 pertrochanteric fractures. Pinning alone was performed in 6 patients, a pin and plate was used in 34 and a Moore's prosthesis was inserted in 13. Patients were not treated with aspirin or other antithrombotic medications during their care.

Functional ascending phlebography was performed principally according to the technique described by Rogoff and DeWeese (1960). After being reassured and coached in details of the procedure, the patient was placed semi-erect on an X-ray table raised to 45° from the horizontal. Percutaneous puncture or cut down was made into any convenient vein on the dorsum of the foot with a 20-gauge scalp vein needle. Infusion of isotonic saline was begun through a three-way stopcock to keep the needle patent. With a rubber tourniquet placed tightly around the ankle, 50 ml of Conray 280 (60 per cent meglumine iothalamate) were injected into the foot vein over a period of 1 min. At the end of the injection, the first exposure was made on a 14 × 34 in. (350 × 855 mm) film at 56 in. (1·4 m) target–film distance. The tourniquet was removed and the patient was instructed to pump up and down on the balls of his feet ten times. A second long radiograph was then exposed. The time lapse between the first and second radiographs was 35–40 s. A third 14 × 17 in. (350 × 427 mm) film centred under the pelvic region was exposed about 45 s after the second radiograph. The patient was then returned to a horizontal position and about 50 ml of saline were rapidly flushed through the needle. The phlebographic examinations were carried out 5–15 days after surgery and 7–28 days after the fracture. The timing of the examinations depended simply upon the availability of the patients and access to the radiological facilities.

All the phlebograms were read and interpreted by one of the authors (S. M. R.) who was unaware of the clinical status of the patients. The criteria for the diagnosis of venous thrombosis were based on those reported by DeWeese and Rogoff (1963), namely: (*a*) the recognition, in at least two radiographs, of well-defined defects in clearly visualized veins; (*b*) lack of opacification of the popliteal, superficial femoral or common femoral veins with good delineation of the proximal and distal veins, and the presence of collaterals. Absence of contrast medium in the calf veins was not considered diagnostic of thrombosis.

Examination for clinical evidence of deep vein thrombosis and pulmonary embolism was made daily by two of the authors (C. K. M. and A. M.). The patients' temperature charts were examined at the same time and attention was paid to any unexplained pyrexia. In the presence of any clinical signs which might suggest pulmonary embolism, a chest X-ray, an electrocardiogram, blood gases, serum bilirubin, serum glutamic-oxaloacetic transaminase and lactic acid dehydrogenase estimations were performed and repeated on subsequent days. Perfusion lung scan was only performed when there was a strong suspicion of pulmonary embolism.

Results

The phlebographic technique proved to be practical and relatively simple to perform. The films were of diagnostic quality, either excluding or demonstrating thrombus. A few patients experienced some discomfort in the foot and calf during the injection of the contrast medium. The discomfort rapidly disappeared after returning the patient to a horizontal position when saline was infused through the veins. There was no allergic reaction to the Conray 280.

Forty-five of the 53 patients who were being studied had bilateral phlebograms. The remaining 8 patients had unilateral phlebograms, 4 on the fractured side alone and 4 on the uninjured limb alone. Thus, there were 49 sets of phlebograms

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Table I: DEEP VEIN THROMBOSIS IN CASES OF FRACTURE OF THE PROXIMAL FEMUR*

Author(s)	Detection methods†	No. in study	Incidence of DVT (%)			Site of thrombi (%)	
			Overall	Injured limb	Uninjured limb	Calf	Above knee
Johnsson et al. (1968)	PG	25	NA	52	NA	NA	NA
Stevens et al. (1968)	PG	71	40	NA	NA	NA	More frequent than calf
Culver et al. (1970)	PG	100	NA	40	50	41·3	58·7
Hamilton et al. (1970)	PG	76		49	26	53·8	46·2
Field et al. (1972)	FUT	50	60	54	34	NA	NA
Kakkar et al. (1972)	FUT	50	54	48	34	NA	NA
Present series	PG	53	53·3	53·1	14·3	84·6	15·4

* Only studies using objective diagnostic criteria are included.
† PG, phlebography; FUT, ^{125}I-labelled fibrinogen uptake test.
NA, Not available.

performed upon injured limbs and another 49 sets upon uninjured limbs.

On reviewing the 49 sets of phlebograms from the injured limbs, thrombi involving the soleal veins were found in 8 patients, the posterior tibial vein in 2, the peroneal vein in another 2 and combinations of these veins in 9. Two patients had isolated clots in the common femoral and superficial femoral veins without calf involvement, and 3 other patients had involvement of both the femoral and calf systems. An incidence of 53·1 per cent of venous thrombosis was diagnosed on the injured limb phlebograms.

Seven (14·3 per cent) of the 49 sets of phlebograms of uninjured limbs were positive for venous thrombosis. There was one case each of soleal and peroneal vein thrombi, 2 patients had posterior tibial vein thrombi and a combination of calf vein involvement was present in 3 other patients.

Fifteen patients with phlebographic thrombi had clinical evidence of deep vein thrombosis; 11 other patients had clinical features of phlebothrombosis but showed no evidence of it on the phlebograms. Fourteen patients who showed evidence of a phlebographic defect had no clinical evidence of thrombosis. There was no diagnosed pulmonary embolism. Clinical features which remotely suggested pulmonary embolism were observed in 2 patients. Investigations, including perfusion lung scans, excluded the diagnosis. There was no hospital mortality in this group of patients.

Discussion

A group of patients with fracture of the proximal femur was selected for the study of venous thromboembolism among Chinese because the inhabitants of Western countries have a high incidence of venous thromboembolism. Despite the clinical observations of 'absence of thromboembolic complications' among Chinese patients with fractures of the proximal femur managed by non-operative (Horn and Wang, 1964) and operative (Bong and Chow, 1977) treatment, an overall incidence of 53·3 per cent of deep vein thrombosis was disclosed by the present phlebographic study. This is similar to that reported in the West (*Table I*).

When confinement to bed is taken as a risk factor, our patients were at a greater risk than similar patients in Western countries. In the present series, because of the lack of operating time, hip surgery was performed 2–14 days after the injury. Although clinical evidence of deep vein thrombosis was carefully sought, a confident clinical diagnosis of deep vein thrombosis was made on only two occasions in this prospective survey. An analysis of the clinical data collected and the phlebographic findings revealed no correlation between them. Inadequacy of the clinical methods probably explains the failure to recognize deep vein thrombosis in Chinese patients with fracture of the proximal femur by both Horn and Wang and Bong and Chow. Two unique observations of these authors remain, i.e. a low mortality rate (5·5 and 3·6 per cent respectively) and the absence of fatal pulmonary embolism. In the present study, when the sites of the thrombi are analysed and compared with similar studies in the West (*Table I*), the following points of difference are evident: (*a*) involvement of the uninjured limb is far less common; (*b*) the majority of thrombi are located in the calf; (*c*) extensive venous thrombosis is not observed. In the autopsy study on pulmonary embolism by Hwang in Singapore (1968), the incidence among Chinese was found to be low and massive emboli were rare. The low incidence of 'clots at risk' (Kakkar et al., 1969) among Chinese patients with fractures of the proximal femur probably explains the absence of clinical and fatal pulmonary embolism observed by us and others. It is felt that the differences demonstrated in this study merit further investigation.

References

BAKER L. W. and HOULDER A. (1973) Deep vein thrombosis in Bantu and Indian patients. *S. Afr. Med. J.* 47, 1689–1692.

BAKER L. W. and PRAJAPAT D. K. (1974) Deep vein thrombosis in African and Indian patients. *S. Afr. J. Surg.* 12, 127–131.

BONG S. C. and CHOW S. P. (1977) Mortality in fractures of the proximal end of femur in Hong Kong Chinese. *J. West Pacific Orthop. Assoc.* 14, 1–8.

CHUMNIJARAKIJ T. (1974) Incidence of postpartum thromboembolism in Thai women: comparison with Western experience. *J. Med. Assoc. Thailand* 57, 592–594.

CHUMNIJARAKIJ T. and POSHYACHINDA V. (1975) Postoperative thrombosis in Thai women. *Lancet* 1, 1357–1358.

COLIN J. F., ROTTCHER K. H. and HALL D. P. (1975) Venous thrombosis in Africans. *Lancet* 1, 408.

CULVER D., CRAWFORD J. S., GARDINER J. H. et al. (1970) Venous thrombosis after fractures of the upper end of the femur. *J. Bone Joint Surg.* 52B, 61–69.

CUNNINGHAM I. G. E. and YONG N. K. (1974) The incidence of post-operative deep vein thrombosis in Malaysia. *Br. J. Surg.* 61, 482–483.

DEWEESE J. A. and ROGOFF S. M. (1963) Phlebographic patterns of acute deep venous thrombosis of the leg. *Surgery* 53, 99–108.

DODD H. (1964) The cause, prevention and arrest of varicose veins. *Lancet* 5, 809–811.

FIELD E. S., NICOLAIDES A. N., and KAKKAR V. V. (1972) Deep vein thrombosis in patients with fractures of the femoral neck. *Br. J. Surg.* 59, 377–379.

FRANZ R. C., KARK A. E. and HATHORN M. (1961) Postoperative thrombosis and plasma fibrinolytic activity. A comparative study in Africans, Indians and Whites. *Lancet* **1**, 195–197.

GORE I., HIRST A. E. and TANAKA K. (1964) Myocardial infarction and thromboembolism. A comparative study in Boston and in Kyushu, Japan. *Arch. Intern. Med.* **113**, 323–330.

HAMILTON H. W., CRAWFORD J. S., GARDINER J. H. et al. (1970) Venous thrombosis in patients with fracture of the upper end of the femur. A phlebographic study of the effect of prophylactic anticoagulation. *J. Bone Joint Surg.* **52B**, 268–289.

HASSAN M. A., RAHMAN E. A. and RAHMAN I. A. (1974) Prostatectomy and deep vein thrombosis in Sudanese patients. *Br. J. Surg.* **61**, 650–652.

HORN J. S. and WANG Y. C. (1964) The mechanism, traumatic anatomy and non-operative treatment of intertrochanteric fracture of the femur. *Br. J. Surg.* **51**, 574–580.

HWANG W. S. (1968) The rarity of pulmonary thromboembolism in Asians. *Singapore Med. J.* **9**, 276–279.

JOFFE S. N. (1974) Racial incidence of postoperative deep vein thrombosis in South Africa. *Br. J. Surg.* **61**, 982–983.

JOHNSSON S. R., BYGDEMAN S. and ELIASSON R. (1968) Effect of dextran on postoperative thrombosis. *Acta Chir. Scand.* Suppl. 387, pp. 80–82.

KAKKAR V. V., HOWE C. T., FLANC C. et al. (1969) Natural history of postoperative deep vein thrombosis. *Lancet* **2**, 230–232.

KAKKAR V. V. (1972) The diagnosis of deep vein thrombosis using the ^{125}I fibrinogen test. *Arch. Surg.* **104**, 152–159.

ROGOFF S. M. and DEWEESE J. A. (1960) Phlebography of the lower extremity. *JAMA* **172**, 1599–1606.

SANDRITTER W. and FELIX H. (1967) Geographical pathology of fatal lung embolism. *Pathol. Microbiol.* **30**, 742.

SEVITT S. (1965) Postoperative prophylactic anticoagulants in gynaecology. *Lancet* **1**, 217.

SRIVASTAVA S. C. (1964) Absence of pulmonary embolism in Asians. *Br. Med. J.* **1**, 772–773.

STEVENS J., FARDIN R. and FREEARK R. J. (1968) Lower extremity thrombophlebitis in patients with femoral neck fractures. *J. Trauma* **8**, 527–534.

TALALAK P. (1976) Thromboembolism in Thailand. Incidence, coagulogram and its significance in therapeutic implication and prognosis. *J. Med. Assoc. Thailand* **59**, 6–11.

THOMAS W. A., DAVIES J. N., O'NEAL R. M. et al. (1960) Incidence of myocardial infarction correlated with venous and pulmonary thrombosis and embolism. A geographic study based on autopsies in Uganda, East Africa and St. Louis. *Am. J. Cardiol.* **5**, 41–47.

TINKLER L. F. (1964) Abscence of pulmonary embolism in Asians? *Br. Med. J.* **1**, 502.

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The average medical book is predominantly textual and illustrations are needed for two reasons: first, to represent something which the reader needs to be able to interpret by sight and not by a verbal description—something he will see in his work and recognize because he has seen it before, such as a measles rash as opposed to smallpox, a radiograph shadow, or a pathological cross-section; secondly, to clarify something which is obscure when expressed in words alone.

Medical illustrations are not designed primarily as decoration. The extent to which pictures are used instead of words can be a reflection of the author's verbal skills, but by and large it is he who originates the thought—the substance—of the book, and it is he who should decide whether it can be expressed best in words or in pictures.

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Thyroid cancer: prognosis in 469 patients

M. D. STAUNTON AND R. G. SKEET*

SUMMARY

A computer study of 469 patients with thyroid cancer is presented. There were 40 per cent anaplastic, 30 per cent papillary, 15 per cent follicular and 15 per cent rarer tumours. The 20-year survival was 7·5 per cent for anaplastic, 55 per cent for papillary and 35 per cent for follicular carcinoma. The dominant role of histology in prognosis is confirmed.

Other important factors are: all patients under 45 reap benefit; females survive longer than males with papillary and follicular tumours. Cervical node metastases confer no depression in papillary tumours. Local tumour advance depresses survival but facilitates diagnosis. We find merit in the TNM classification, but warn against overelaboration.

We regret our failure to assess the differential effect of individual treatment, which poses a continuing challenge to oncologists.

ACCURACY in prognosis allows rational management of cancer. For common cancers, such as those of the lung or stomach, it required years of labour to achieve the present degree of knowledge of their behaviour. So much more difficult is it to reach the same level of knowledge about a rare cancer, such as that of the thyroid, with the added difficulty of its many variants. Thus, there is a need for reports on thyroid cancer from as many centres as possible, particularly from hospitals where relatively large numbers are treated and the patients are followed through life.

Patients and methods

A total of 535 patients with malignant neoplasms of the thyroid was treated at the Royal Marsden (formerly Royal Cancer) Hospital, London, between 1931 and 1972. Past reports on this work are listed elsewhere (Staunton and Greening, 1976). We studied all the original case notes and transferred the relevant facts to a proforma. At the South Thames Cancer Registry the information was analysed by computer. The follow-up information extends to 1976. Histological classification followed the principles of Meissner and Warren (1969). Professor Gowing reviewed all the original slides where the clinical course cast any doubt on the initial diagnosis. We excluded 66 cases of malignant adenoma, considering them benign (Staunton, 1976), and review here 469 patients with thyroid cancer.

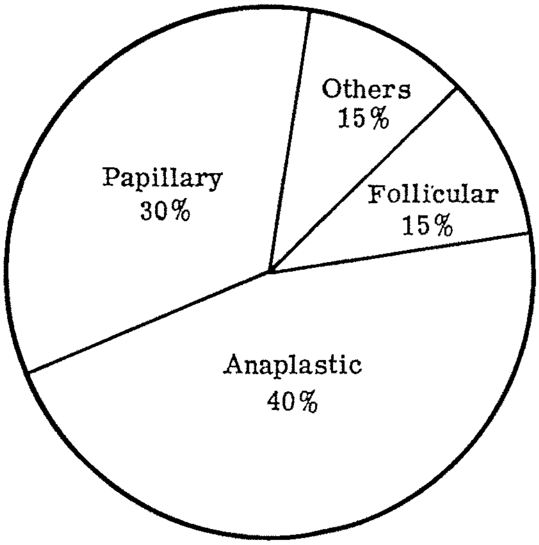

Fig. 1. Distribution of histological types.

Table I: AGE AND SEX DISTRIBUTION BY EACH TUMOUR TYPE

Type	Sex M	 F	Total	%	Average age (yr)
Papillary	41	106	147	31	45·6±2·8
Follicular	15	58	73	16	53·4±3·4
Anaplastic	49	116	165	35	61·9±2·1
Lymphosarcoma	3	29	32	7	60·8±5·8
Medullary	5	7	12	3	52·1±11·4
Fibrosarcoma	1	0	1	0	63·0
No histology	12	27	39	8	63·6±4·3
Total	126	343	469	100	55·3±1·6

Table I shows the number of each tumour type with the sex distribution and average age. The behaviour of those without histology confirms the clinical opinion that they were, in the main, anaplastic tumours. Thus, the approximate percentage of differing types was: anaplastic 40 per cent, papillary 30 per cent, follicular 15 per cent and others 15 per cent (these include lymphosarcoma and medullary carcinoma). We confine this report to the three main types shown in *Fig.* 1. The high percentage of anaplastic tumours makes the series unusual; only Scott and Halnan (1974) from Glasgow have a similar distribution. North American reports give papillary carcinoma an approximately two-thirds share, with anaplastic carcinoma the least frequent. Three reports from London (Greene, 1969; Taylor and Davies, 1970; Beaugie et al., 1976) also found papillary tumours to be most common. These differences call for comment. We know that in endemic goitre areas follicular carcinoma is the commonest type (Cuello et al., 1969) and in such areas, following iodine prophylaxis, an increasing papillary carcinoma rate is found (Heitz, 1976). Williams and Doniach (1976) made the interesting point that areas of high iodine content, such as Iceland, have a high percentage of papillary tumours in contrast to Aberdeen (low iodine), where anaplastic cancer is more frequent. It is well known that many differentiated tumours progress to anaplastic, so a 'late' series would contain a higher incidence of anaplastic than an 'early' one. Other factors could be the quirks of hospital selection and differences in histological classification. Whatever the reason, conflicting conclusions from differing series require careful scrutiny.

Various factors and their effect on prognosis were evaluated by computing actuarial survival rates and calculating the standard error at 5 years by the method of Greenwood (1926). The rates are 'minimum survival rates' since no account was taken of the fact that some deaths were due to causes other than thyroid cancer. For the detailed analysis the 5-year survival rate was used. Beyond 5 years, when the data had been divided into the various subgroups, the number of patients at risk was often too small to obtain reliable survival rates.

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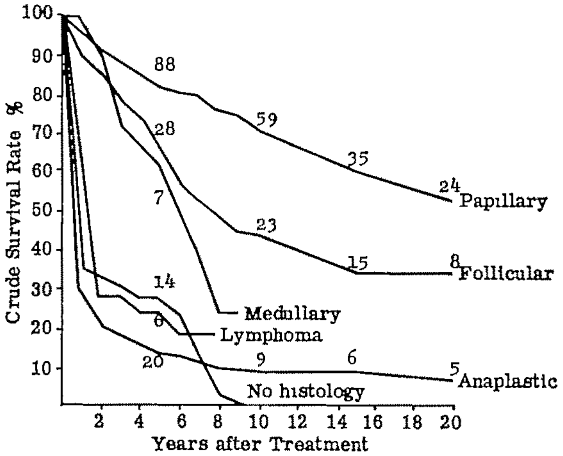

Fig. 2. Twenty-year survival rates by histological type.

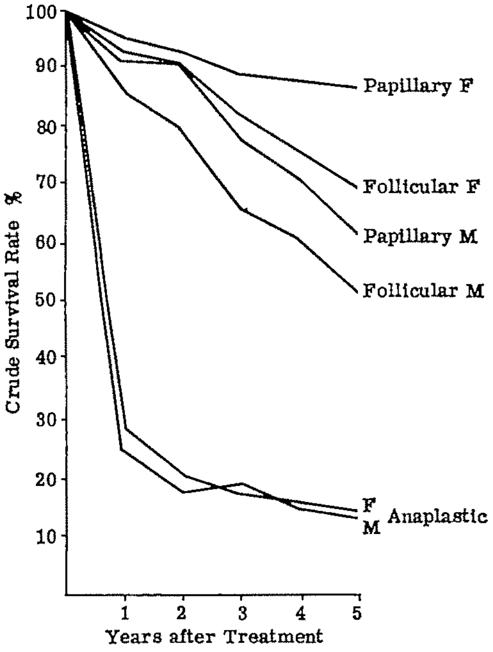

Fig. 3. Survival by histology and sex.

Fig. 2 shows the crude 20-year survival of this series (1931–72) in percentages, namely, papillary tumours 55 per cent (24 patients surviving), follicular tumours 35 per cent (8 patients surviving) and anaplastic tumours 7·5 per cent (5 patients surviving). The comparable figures of the 1931–61 series were 39, 23 and 4 per cent respectively (Staunton and Greening, 1976).

Results

The dominant role of histological type in prognosis was revealed by Woolner et al. (1961), and thus the findings in *Fig.* 2 cause no surprise but add further support to those authors' now classic account. The three main types of carcinoma gave statistically significant differences in survival: papillary better than follicular ($P<0{\cdot}05$), papillary better than anaplastic ($P<0{\cdot}0001$) and follicular better than anaplastic ($P<0{\cdot}0001$).

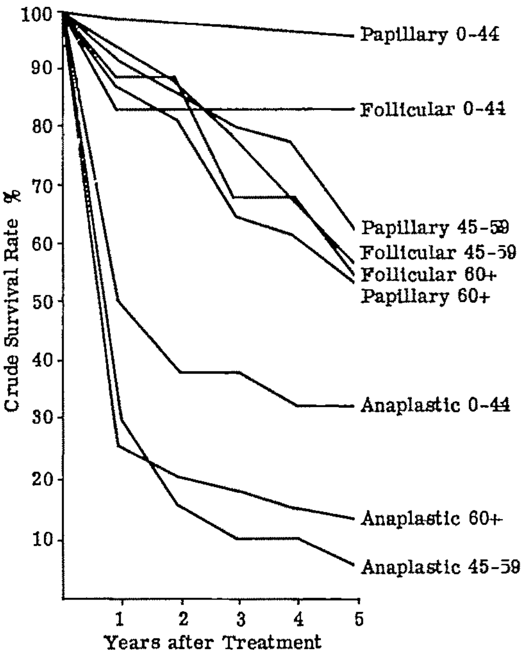

Fig. 4. Survival by histology and age group.

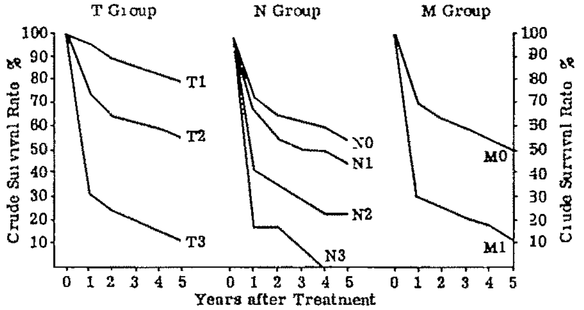

Fig. 5. Survival by TNM classification.

The part played by sex is illustrated in *Fig. 3.* Women with papillary tumours have a significantly longer survival ($P<0{\cdot}0001$). Females with follicular tumours seem to live longer but to a degree which just misses significance. In anaplastic carcinoma sex confers no benefit.

Fig. 4 shows the effect of age on survival rate, dividing the data into three age groups at 45 and 60 years. Crile's (1953) original opinion that age had a significant effect on survival was strongly supported in the young, i.e. those under 45. The survival of the young papillary group was significantly better than that of the middle aged or elderly ($P<0{\cdot}0001$); results were similar in follicular and anaplastic tumours ($P<0{\cdot}05$), granted the small number in the young anaplastic group. A new observation suggests that the middle aged have no improvement in survival over the elderly in any of the three types. Thus, age confers benefit only under 45 years and is not related to histology. The latter exercises a stronger effect, as shown in *Fig.* 4, where the worst (i.e. the oldest) papillary fare better than the best (i.e. the youngest) anaplastic.

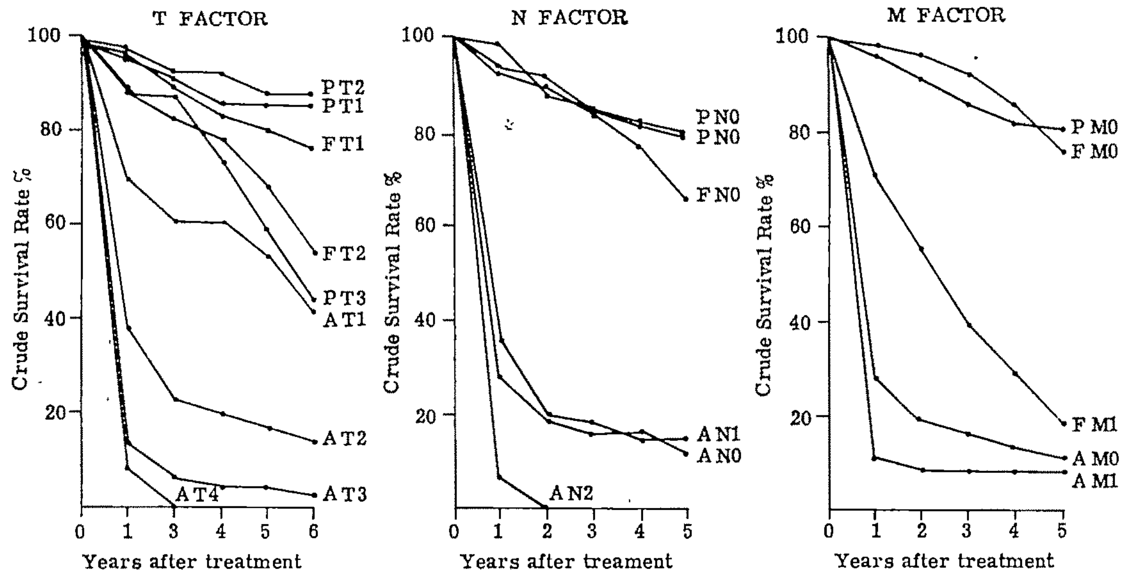

Fig. 6. Survival by histology and TNM classification.

Clinical factors

We give the computed 5-year survival rates by clinical findings in *Table II*. Patients with mobile tumours live longer ($P<0{\cdot}0001$) than those with either tethered or fixed tumours; those with tumours with smooth surfaces fared better ($P<0{\cdot}0001$) than those with nodular tumours; patients with tumours which were cystic or elastic did better ($P<0{\cdot}0001$) than hard tumours. From X-ray evidence it seemed that tracheal deviation or compression reduced survival ($P<0{\cdot}0001$), as also did vocal cord oedema or paralysis on laryngoscopy. Patients with tumours which were intrathyroid at operation lived longer than those with extrathyroid tumours ($P<0{\cdot}0001$).

The T (primary tumour), N (regional nodes), M (metastases) system of classification proposed by Denoix in 1953 was adopted by the International Union against Cancer (UICC) and applied to many sites, including the thyroid. *The TNM Classification of Malignant Tumours* (Geneva, 1968) is followed in this paper. After the XII International Congress in Buenos Aires (1978) a revised classification was published, based on the recommendations of the European Organization for Research on Treatment of Cancer (EORTC) and this may be found in the third edition of the booklet. We staged all patients where the case notes carried adequate details.

Fig. 5, taking all types of thyroid cancer together, gives survival by TNM. In T and M each stage carries a significant difference ($P<0{\cdot}0001$). In N the differences between N^0 and N^1 lacked significance; but N^2 behaved significantly worse than either ($P<0{\cdot}01$); while N^3 cases (fixed nodes) were too few for analysis. Taking a lead from the third edition of *The TNM Classification of Malignant Tumours* we staged our tumours under each histological type. *Fig.* 6 gives the results. This shows that T and M give worthwhile forecasting by emphasizing the perils of local advance and blood-spread metastases in all types. Again in both papillary and anaplastic tumours no significant difference occurs between N^0 and N^1, while lack of numbers precluded analysis of N^2 and N^3.

Table II: 5-YEAR SURVIVAL RATES BY CLINICAL FINDINGS

Sign or investigation	Findings	No. of cases initially at risk	5-yr survival rate (%)
Tumour mobility	Free	272	68
	Tethered	74	20
	Fixed	73	8
Tumour extent	Confined	302	61
	Extrathyroid	66	25
	Retrosternal	82	18
Stridor	Absent	423	52
	Present	62	18
Clinical assessment of cervical nodes	Impalpable	379	54
	Mobile	85	41
	Fixed	23	17
Consistency	Cystic	37	77
	Elastic	143	63
	Hard	207	28
Surface	Smooth	149	72
	Nodular	250	34
Oesophagus (barium swallow)	Normal	178	73
	Deviated	26	12
	Compressed	121	18
Trachea X-ray	Normal	104	75
	Deviated	185	43
	Compressed	44	11
Thyroid X-ray	Normal	24	65
	Abnormal	45	19
Laryngoscopy	Normal	263	69
	Oedema	31	13
	Cord paralysed	71	17

Pathology factors

Pure papillary and follicular tumours allow easy classification, but as many cases exhibit both elements many clinicians considered their segregation futile and reported the entire group as 'differentiated'. Woolner's (1961) plea for their divorce is well supported here. Eighty-two per cent of patients with tumours showing both elements survive to 5 years, similar to those with pure papillary tumours—establishing that the papillary element begets behaviour. Thus it is right to class as papillary all tumours exhibiting any papillary element.

We include Hürthle cell tumours under follicular and note the increased survival associated with them —78 per cent at 5 years against 63 per cent for the total follicular group. This differing survival justifies the continued identification of the Hürthle cell tumours and, should similar results be reported from other centres, then, from the view of prognosis, Hürthle cell tumours would be better classified among papillary tumours. The presence of anaplastic elements depresses survival among patients with papillary tumours to 40 per cent at 5 years and, among follicular tumours, to 30 per cent. Progression from differentiated to anaplastic has occurred in 19 patients, all dying from anaplastic metastases. The incidence of progression was 3 per cent in those treated without radiotherapy and 12·5 per cent in those with ($P<0·5$). Associated thyroiditis, shown histologically, conferred increased survival of 49 per cent at 5 years against 25 per cent in those without thyroiditis ($P<0·05$). The rate of mitosis exerted a powerful influence: where frequent, only 20 per cent survived 5 years as against 75 per cent where infrequent.

On the other hand, the following differences lack significance. Blood vessel invasion in patients with papillary tumours achieved a 70 per cent survival at 5 years against 80 per cent survival in those without invasion; blood vessel invasion in those with follicular tumours gained 72 per cent survival against 73 per cent in those without; lastly, those with anaplastic tumours with vessel invasion had 13 per cent survival against 17 per cent in those without. Capsular invasion was reported in only a quarter of cases, making analysis meaningless.

Nodal metastases were present in 47 per cent of papillary, 19 per cent of follicular and 46 per cent of anaplastic tumours. Five-year survival in these cases was 81 per cent, 61 per cent and 13·6 per cent respectively, in contrast to 73·4 per cent, 70·3 per cent and 11·1 per cent without node metastases. The differences lacked significance, confirming the view quite exceptional in oncology, that node metastases fail to depress survival; in fact, in papillary carcinoma they confer a slight advantage, possibly reflecting a high anti-tumour response rather than a late stage in the disease.

Discussion

Our results agree to a surprising extent with previous studies. Common histological classification allows comparison of like with like, disparities revealing areas for further investigation. Histology confirms that patients with papillary tumours survive longer than those with follicular tumours, and that both survive much longer than patients with anaplastic carcinoma.

Anaplasia confers increased malignancy in all cancers, therefore that it has a similar effect in the thyroid is not remarkable, but it is more difficult to explain why, with papillary tumours, prognosis is relatively good. A partial answer is because many such cancers occur under the age of 45, when age has a beneficial effect. This begs the question why should age exert a beneficial effect here when it does not do so in other cancers at the same age? We do not know, but the answer may be found in the hormonal factors surrounding and the high antigenicity contained in the papillary cell, manifest in the florid node metastases, such as feature in the young, and the favourable response to thyroxine. The differing prognosis of papillary and follicular tumours must be linked to their differing behaviour, e.g. the local displacement of surrounding tissues by follicular tumours against the infiltration of papillary tumour; the scarcity of nodal metastases with early blood spread so characteristic of follicular tumours as against early node metastases and late blood spread in papillary tumours. Histologically, the papillary tumour stimulates surrounding cellular reaction, notably absent in follicular tumours.

Another problem is the progression from low grade to anaplastic. This occurs in all cancers, but is more remarkable in the thyroid as it transforms the most docile of tumours into a lethal one. Why? The easy answer is continuing exposure to carcinogens. One proved carcinogen is radiation. The natural progression rate of 5 per cent (Thomas, 1972) fits well with the 3 per cent found here in those not given radiation, but 12·5 per cent found in those given such treatment must raise the question of whether the treatment increased the carcinogenic effect. The small numbers preclude any conclusion, but the message must be one of caution in the use of radiation for a tumour with a long natural history, particularly in a young person, unless other measures have failed.

Age

Most authors (Halnan, 1966; Bell, 1975; Russell et al., 1975; Cady, 1976) agree with Crile (1953) that increasing age carries an inverse relationship to survival. McKenzie (1971) found the effect limited to 'differentiated' tumours; Franssila (1975) agreed, but only in follicular cancers did this reach significance. Adding our own findings, the collective evidence points to a universal significant age factor before 45, exerting greater influence on papillary and follicular than on anaplastic types. Afterwards the effect wanes to insignificant levels in all cancer types.

Sex

Woolner et al. (1961), Halnan (1966), Hirabayashi and Lindsay (1961) and Beaugie et al. (1976) all failed to find any influence by sex on survival. Doll (1969), from a collective review, found with anaplastic tumours that male cases fared worse than female cases, but not to a significant degree; while with both papillary and follicular tumours the female advantage was significant. Franssila (1975) found that female patients with follicular tumours live longer, but not significantly so. Campbell and Sage (1975) and Cady (1976) found males to have reduced survival. We find, as did Doll (1969), that males with papillary tumours have a significantly improved survival, those with follicular tumours an improved survival, but not significantly so and in those with anaplastic tumours there is no advantage. Thus, the evidence fails to agree, but it may be a pointer that since Doll's report (1969) only one study has failed to find a relationship between females and prolonged survival in 'differentiated' tumours, but this effect is a lesser one than age.

At first we hoped to show the influence of treatment, in particular the role of surgery, on prognosis. To our disappointment, although we had large groups and comparable treatment groups, the large groups were not comparable and the comparable groups were too small to be significant. Nevertheless, we are heartened by the improved results here against those of the earlier series (1931–62), reflecting at least in part improved treatment. This merits further study.

Surgeons are well aware of the marked differences in survival between histological groups, but perhaps not so aware of the influences of age, local advance and the benign effects of nodes in papillary tumours—factors which are obvious on first encounter and critical on the ultimate outcome. Armed with these guidelines, the surgeon can match benefit against risk for the welfare of each patient.

Acknowledgements

We thank Mr R. W. Raven, Sir David Smithers, Mr M. H. Harmer and Mr W. P. Greening who gave permission to publish their cases and were a source of continuous help and inspiration. Thanks also go to Miss M. Martin, who designed and carried out the computer conversion, to Miss Susan Taylor and Mrs E. Strong for retrieval of records and to Professor Noel Gowing for generous advice.

References

BEAUGIE J. M., BROWN C. L. and DONIACH I. (1976) Primary malignant tumours of the thyroid. *Br. J. Surg.* **63**, 173–181.

BELL G. C. (1975) Cancer of thyroid prognosis. *Med. Clinics North Am.* **59**, 459–470.

CADY B. (1976) Changing clinical, pathologic, therapeutic and survival in differentiated thyroid carcinoma. *Ann. Surg.* **184**, 541–552.

CAMPBELL D. J. and SAGE R. H. (1975) Thyroid carcinoma—20 years experience in a general hospital. *Br. J. Surg.* **62**, 207–214.

CRILE G. jun. (1953) Relationship of age to natural history and prognosis in thyroid cancer. *Ann. Surg.* **138**, 33–38.

CUELLO C., CORREA P. and EISENBERG H. (1969) Geographic pathology of thyroid carcinoma. *Cancer* **23**, 230–239.

DOLL R. (1969) In: HEDINGER C. E. (ed.) *Thyroid Cancer.* London, Heinemann, p. 309 (UICC Monograph).

FRANSSILA K. O. (1975) Prognosis in thyroid cancer. *Cancer* **36**, 1138–1146.

GREENE R. (1969) Treatment of thyroid cancer. *Br. Med. J.* **4**, 787–789.

GREENWOOD M. (1926) Natural duration of cancer. *Reports on Health and Medical Subjects*, No. 33. London, HMSO.

HALNAN K. E. (1966) Age and sex in thyroid cancer. *Cancer* **19**, 1534.

HEITZ P. (1976) A study in thyroid cancer. *Cancer* **37**, 2329–2337.

HIRABAYASHI R. N. and LINDSAY S. (1961) Carcinoma of thyroid: a study of 390 patients. *J. Clin. Endocrinol.* **21**, 1596–1610.

MCKENZIE A. D. (1971) Natural history of thyroid cancer. *Arch. Surg.* **102**, 274–277.

MEISSNER W. A. and WARREN S. (1969) *Tumours of the Thyroid Gland.* Armed Forces Institute of Pathology, Washington.

RUSSELL M. A., GILBERT E. F. and JAESCHKE W. F. (1975) Prognostic features of thyroid cancer. *Cancer* **36**, 553–559.

SCOTT J. S. and HALNAN K. E. (1974) Thyroid cancer. *Proc. R. Soc. Med.* **67**, 1106–1108.

STAUNTON M. D. (1976) Malignant adenoma of thyroid: hail or farewell? *Clin. Oncol.* **2**, 157–159.

STAUNTON M. D. and GREENING W. P. (1976) Treatment of thyroid cancer in 293 patients. *Br. J. Surg.* **63**, 253–258.

TAYLOR S. and DAVIS P. W. (1970) In: SMITHERS D. (ed.) *Tumours of Thyroid Gland.* Edinburgh, Livingstone.

THOMAS C. G. jun. (1972) In: SABISTON D. C. (ed.) *Davis-Christopher Textbook of Surgery.* Philadelphia, Saunders.

WILLIAMS E. D. and DONIACH I. (1976) Thyroid carcinoma in an iodine risk area. *Cancer* **39**, 215–222.

WOOLNER L. B., BEAHRS O. H., BLACK B. M. et al. (1961) Classification and prognosis in thyroid cancer. *Am. J. Surg.* **102**, 354–387.

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Hyperparathyroidism in pregnancy

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SUMMARY

Primary hyperparathyroidism in pregnancy is uncommon and easily overlooked. It is associated with a complication rate of up to 80 per cent—mainly stillbirths, abortions and neonatal tetany. Surgical treatment during pregnancy offers the best chance for fetal and neonatal survival.

HYPERPARATHYROIDISM occurring during pregnancy is very rare. However, this entity may be recognized more frequently with the routine use of the automated biochemical analyser.

This disease is associated with high maternal and fetal morbidity and of great importance is the apparent lack of awareness by many doctors that hyperparathyroidism can occur during pregnancy. We report here 3 cases that illustrate most of the features of this condition.

Case reports

Case 1: C. K., a 24-year-old Indian, was transferred to Hammersmith Hospital on 24 April 1975, 2 weeks after a Caesarean section at term for transverse lie. She had been perfectly fit but developed progressive weakness and fatigue during the pregnancy and during the last trimester complained of pains in the ribs, hips and back. On the fifth day post partum her baby developed some 'twitching' and was found to be hypocalcaemic. It was only at this stage that the mother was investigated and found to be grossly hypercalcaemic.

On admission she was extremely ill and complained of thirst, nausea and skeletal pains. She was emaciated and had a small swelling on the right side of her neck in the thyroid region. There was marked hyper-reflexia and bony tenderness, and she was unable to lift her limbs from the bed.

Relevant investigations were as follows: serum calcium 3·8 mmol/l (normal 2·15–2·65); serum phosphorus 1·1 mmol/l (normal 0·8–1·4); total proteins 66 g/l (normal 65–80); alkaline phosphatase 1155 i.u./l (normal 30–130); serum magnesium 0·3 mmol/l (normal 0·8–1·2). X-rays of her hands showed marked subperiosteal erosions, bone resorption and early cyst formation and X-ray of the skull showed a classic 'pepper-pot' effect.

An attempt to control her hypercalcaemia was made using calcitonin intravenously, a fluid diuresis and oral phosphates. Her magnesium deficiency was also corrected. However, despite good rehydration, the calcium level could not be controlled and on the third day after admission surgical exploration of the neck was performed. A parathyroid adenoma 3×2·5×2 cm was removed from the lower right position. Postoperative recovery was complicated by hypocalcaemia which was controlled with calcium gluconate i.v. and she received oral calcium and vitamin D for a further 2 months. Her recovery was complete and she remains normocalcaemic. In 1978 she had a normal pregnancy and delivery with no complications.

Case 2: G. K., an Indian doctor, had had three previous miscarriages before the present pregnancy which was also complicated by a threatened abortion at 11 weeks and a premature birth at 35 weeks. Three days post partum the baby developed tetany, due to hypocalcaemia. Investigation of the mother showed a normal serum calcium and phosphorus level and a raised alkaline phosphatase. She was thought to have mild osteomalacia due to an inadequate intake of vitamin D during her pregnancy, and she was treated with a short course of the vitamin.

Two months after completing this course her serum calcium level had risen to 2·8 mmol/l (normal 2·15–2·65) and her serum phosphorus was at the lower limit of normal. The results of other biochemical estimations were normal. The serum parathyroid hormone (PTH) level was 1·1 μg/l (normal <0·75). A diagnosis of primary hyperparathyroidism was made and, at operation, a small parathyroid adenoma (0·5×0·4×0·2 cm) was removed from the left upper position. The patient made a satisfactory recovery and her serum calcium remains in the normal range.

Case 3: A. C., a 36-year-old English woman, had had two normal pregnancies—the last 11 years previously. During 1976 and 1977 she had had several attacks of renal colic and was eventually investigated and found to have hypercalcuria and mild hypercalcaemia (Ca^{2+} 2·7 mmol/l) thought to be due to mild primary hyperparathyroidism. The serum calcium levels were controlled at that time by dietary measures alone. However, when she became pregnant it was felt that she should have surgical treatment of the hyperparathyroidism and at 22 weeks' gestation she had an adenoma of the parathyroid (1·5×0·7×0·5 cm) removed from the left lower position. Apart from a little temporary hypocalcaemia which was treated with oral calcium supplements she made an uneventful recovery. She continued on oral calcium for the rest of her pregnancy and had a normal delivery at full term of a healthy female baby. There were no neonatal complications.

Discussion

Calcium metabolism undergoes widespread changes in the mother during pregnancy which are reflected by a rise in the level of calcitonin throughout and also of PTH in the latter half of the pregnancy. In addition, calcium absorption from the gut is normally increased in order to compensate for the transfer of 20–30 g of calcium from mother to fetus, mostly in the last trimester. It is not surprising therefore that a rise in circulating PTH due to a parathyroid adenoma is likely to have severe consequences in a patient whose skeleton is already being depleted by the demands of the fetus. If, in addition, the patient is lacking in vitamin D because of an inadequate intake in the diet and lack of sunshine then the health of both mother and fetus is endangered.

While calcium ions move freely across the placenta, serum PTH cannot cross from mother to fetus (Garel and Dumont, 1972; Northrop et al., 1974). Raised maternal calcium levels therefore cross the placenta and cause an increased circulating calcium concentration in the fetus (Wagner et al., 1964) and this in turn will cause suppression of the fetal parathyroids (Sinclair, 1942; Bruce and Strong, 1955).

Bakwin (1937) suggested that the fall in fetal circulating calcium which occurs shortly after birth is due to underactivity of the parathyroid in the newborn which is related to the physiological hyperactivity of the maternal parathyroid during pregnancy. Friderichsen (1939) described tetany in a 5-month-old suckling baby which led to the diagnosis of hyperparathyroidism in the mother, and Talbot et al. (1952) and Walton (1954) described neonatal tetany in children of hyperparathyroid mothers.

Neonatal tetany drew attention to the correct diagnosis in our *Cases* 1 and 2.

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Table I: PARATHYROIDECTOMY DURING PREGNANCY: REPORTED CASES

Author	Symptoms	Gestation at time of op.	Maternal complications	Neonatal complications
Petit and Clark (1947)	Renal colic	6 mth	None	None
Whalley (1963)	Polyuria, renal stones, weakness	6 mth	Spout-abortion, hypocalcaemic	Macerated fetus
Goldsmith et al. (1966)	Bone pain	N.S.	Tetany	N.S.
Rubin et al. (1968)	Asymptomatic	2nd trim.	None	None
Findlay (1969)	Renal colic	24 wk	Pre-eclamptic toxaemia at 38 wk	None
Dobbelstein et al. (1970)	Thirst, weakness	7 mth	Hypocalcaemia	None
Johnstone et al. (1972)	N.S.	3 mth	Tetany, Caesarean section (disproportion)	None
Beal (1974)	Nausea, vomiting, lethargy	2 mth	N.S.	None
Pedersen and Permin (1975)	Renal colic	14 wk	Normal delivery at 36 wk	None
Dorey and Gell (1975)	Bony tenderness	37 wk	Hypocalcaemia	None
Molinatti et al. (1975)	Asymptomatic	7 mth	Hypocalcaemia, Caesarean section (tranverse lie)	None
Delmonico et al. (1976)	Asymptomatic	4 mth	Caesarean section (disproportion)	None
Gaeke et al. (1977)	Hypertension, nephrocalcinosis	17 wk	Hypocalcaemia	None
Present case	Renal colic	20 wk	Hypocalcaemia	None

N.S., Not stated; trim., trimester.

Case 1 illustrates how symptoms of hyperparathyroidism may be overlooked and blamed on 'the pregnancy' or 'nerves'. Pedersen and Permin (1975) noted that hyperemesis gravidarum may be associated with primary hyperparathyroidism. *Case* 1 also shows how, in the extremely ill patient, attempts to lower the calcium medically are only temporary and may buy a little time before definitive treatment, but if there is no immediate response then parathyroidectomy must be undertaken as a matter of extreme urgency.

Ludwig (1962), in his review of the literature, found a complication rate of 50 per cent in 40 pregnancies in 21 mothers with primary hyperparathyroidism (stillbirths, spontaneous abortion, neonatal deaths 31 per cent, neonatal tetany 19 per cent). Delmonico et al. (1976) found the complication rate to be 80 per cent in the 13 cases described.

Case 2 illustrates many of these complications, i.e. miscarriages, threatened abortion, premature birth, neonatal tetany. This case also shows how the diagnosis of hyperparathyroidism may be masked biochemically by osteomalacia due to deficiency of vitamin D in the diet.

That surgical treatment of primary hyperparathyroidism can be undertaken during pregnancy is shown by *Case* 3. Since Petit and Clark (1947) described their successful removal of a parathyroid adenoma during pregnancy there have been a further 13 similar cases (including our own) described in the literature (*Table I*). In these 14 cases complications have been few. In Whalley's case (1963) spontaneous abortion of a macerated fetus occurred the day after parathyroidectomy which was performed for a hyperparathyroid crisis with associated renal stones and hypertension in which the fetus was dead before operation. There were no other neonatal complications in this group, except hypocalcaemia without tetany in Delmonico's case (Delmonico et al., 1976).

Maternal postoperative hypocalcaemia required treatment in at least 8 of these 14 cases, indeed tetany developed in 2 cases. We would advocate careful postoperative monitoring of the serum calcium level and treatment with calcium supplements should the calcium fall below the normal range even if symptoms of hypocalcaemia are not present. With such a high risk of maternal hypocalcaemia perhaps calcium supplements should be given routinely and continued for the rest of pregnancy.

It would seem that operative treatment of hyperparathyroidism in pregnancy is the treatment of choice, reducing considerably the neonatal morbidity.

References

BAKWIN H. (1937) Pathogenesis of tetany of the newborn. *Am. J. Dis. Child.* **54**, 1211–1226.

BEAL J. (1974) Hyperparathyroidism and pregnancy. *Ill. Med. J.* **145**, 520.

BRUCE J. and STRONG J. A. (1955) Maternal hyperparathyroidism and parathyroid deficiency in child. *Q. J. Med.* **24**, 307–319.

DELMONICO F. L., NEER R. M., COSINI A. B. et al. (1976) Hyperparathyroidism during pregnancy. *Am. J. Surg.* **131**, 328–337.

DOBBELSTEIN H., PICHLMAIER H. and KARL H. J. (1970) Primarer Hyperparathyreoidismus in der Schwangerschaft. *Internist* **11**, 139–142.

DOREY L. G. and GELL J. W. (1975) Primary hyperparathyroidism during the third trimester of pregnancy. *Obstet. Gynecol.* **45**, 469–472.

FINDLAY W. S. (1969) Hyperparathyroidism complicating pregnancy. *Proc. R. Soc. Med.* **62**, 835.

FRIDERICHSEN D. (1939) Tetany in a suckling with latent osteitis fibrosa in the mother. *Lancet* **1**, 85–86.

GAEKE R. F., KAPLAN E. L., LINDHEIMER M. D. et al. (1977) Maternal primary hyperparathyroidism of pregnancy. *JAMA* **238**, 508–509.

GAREL J. M. and DUMONT C. (1972) Distribution and inactivation of labelled parathyroid hormone in rat fetus. *Horm. Metab. Res.* **4**, 217–221.

GOLDSMITH R. E., ZALME E. and WEINSTEIN A. S. (1966) Clinical experience with primary hyperparathyroidism: evaluation of treatment. *Acta Endocrinol.* **52**, 221–238.

JOHNSTONE R. E. II, KREINDLER T. and JOHNSTONE R. E. (1972) Hyperparathyroidism during pregnancy. *Obstet. Gynecol.* **40**, 580–585.

LUDWIG G. D. (1962) Hyperparathyroidism in relation to pregnancy. *N. Engl. J. Med.* **267**, 637–642.

MOLINATTI G. M., LOSANA O. and ISAIA G. C. (1975) Iperparatiroidismo in gravidanza. *Minerva Med.* **66**, 66–71.

NORTHROP G., MISENHIMER R. H. and BECKER F. O. (1974) Failure of parathyroid hormone to cross the sub-human primate placenta. *Endocrinology* **94**, Suppl. A279.

PEDERSEN N. T. and PERMIN H. (1975) Hyperparathyroidism and pregnancy. *Acta Obstet. Gynaecol. Scand.* **54**, 281–283.

PETIT D. W. and CLARK R. L. (1947) Hyperparathyroidism and pregnancy. *Am. J. Surg.* **74**, 860–866.

RUBIN A., CHAYKIN L. and LUDWIG C. D. (1968) Maternal hyperparathyroidism and pregnancy. *JAMA* **206**, 128–130.

SINCLAIR J. G. (1942) Fetal rat parathyroid as affected by changes in maternal serum calcium and phosphorus through parathyroidectomy and dietary control. *J. Nutr.* **23**, 141–152.

TALBOT N. B., SOBEL E. H., MCARTHUR J. W. et al. (1952) *Functional Endocrinology from Birth through Adolescence.* Cambridge, Mass., Harvard University Press, p. 118.

WAGNER G., TRANSBOL I. and MELCHIAR J. C. (1964) Hyperparathyroidism and pregnancy. *Acta Endocrinol.* **47**, 549–564.

WALTON R. L. (1954) Neonatal tetany in two siblings effect of maternal hyperparathyroidism. *Pediatrics* **13**, 227–234.

WHALLEY P. J. (1963) Hyperparathyroidism and pregnancy. *Am. J. Obstet. Gynecol.* **86**, 517–521.

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Bilateral axillary artery aneurysms in a child

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Case report

Two pulsating lumps were noticed in the axillae of a 10-month-old boy. He had no relevant past history except for a severe encephalitis requiring 3 weeks' hospitalization a month before the appearance of the axillary lumps. On examination the lumps were clearly fusiform aneurysms of the axillary arteries and as the right aneurysm was said to be enlarging, it was explored when the child was 1 year old. A well-localized fusiform true aneurysm was found, surrounded by the trunks of the brachial plexus. When the aneurysm was opened through a longitudinal arteriotomy, it appeared to have a normal adventitia with a thick, white, organized mucinous core (*Fig.* 1). This core seemed to merge with the normal-looking inner layers of the entry and exit vessels. Since the defect was very localized, the aneurysm was resected and the artery reconstructed, using the trimmed normal-looking adventitia and outer layer of the media. The child made an uneventful postoperative recovery.

Histology showed that the inner wall of the aneurysm consisted of loose myxomatous tissue composed of fibrocytes with oval or stellate nuclei and associated fine collagen fibrils separated by a mucinous background which stained strongly with alcian blue. The external wall consisted of media and adventitia, with only a little overlying intima, this last showing changes as described above. There was marked disorganization of the media, with severe degeneration and loss of elastic and muscle fibres, those remaining being separated by a mucinous background. The adventitia was moderately thickened by mature collagen. The vasa vasorum appeared normal and there was no evidence of inflammation. The appearances were those of fibromuscular dysplasia with aneurysm formation.

This case did not have the characteristic clinical features of any recognized type of aneurysm. Congenital aneurysms are usually saccular herniations of the inner layer and are almost always in the cerebral vessels. There were none of the clinical features of either the Marfan or the Ehlers–Danlos syndrome. There was no history of trauma and the aneurysms were not false. Cystic medial necrosis is very rare at this age and almost always affects the aorta. There was no biochemical evidence of either haemocystinuria or a lipodystrophy. As the aneurysms were first noticed shortly after the encephalitis, mycotic aneurysms had to be considered, although these are very rarely due to viral emboli and almost always result in a false aneurysm at a bifurcation of an artery.

Histological evidence strongly suggests that these aneurysms formed on the basis of arterial fibromuscular dysplasia. Similar histological appearances have been described in the basilar artery of an 11-year-old girl who died when the aneurysm ruptured spontaneously (Hirsch and Roessmann, 1975). A 16-month-old boy died following thrombosis of a carotid artery and was also found to have a fusiform aneurysm of the brachial artery due to fibromuscular dysplasia (Duffy et al., 1957). Similar appearances have been described in the neck arteries of 3 other children (Bostrom and Liliequist, 1967), but four-vessel angiography showed no abnormality in our case. The patient still has the axillary aneurysm on the left and the best treatment for this remains uncertain as we were unable to find any information about the natural history of such lesions. Whether the type of plastic reconstruction used on the right is the preferred technique is also debatable; an autologous vein graft may have been a better procedure.

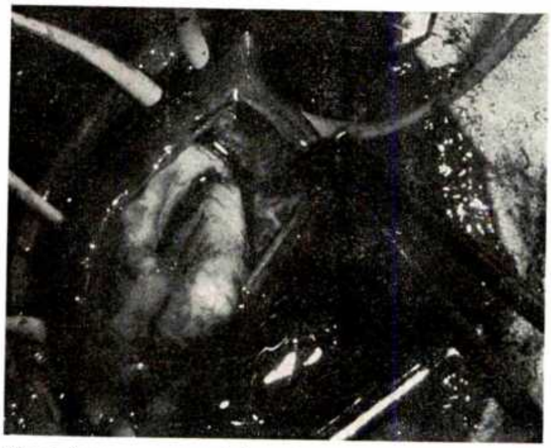

Fig. 1. Aneurysm opened through a longitudinal incision. This thickened inner layer has been cut across and half removed. Branches of the brachial plexus can be seen surrounding the aneurysm.

References

BOSTROM K. and LILIEQUIST B. (1967) Primary dissecting aneurysm of the extracranial part of the internal carotid and vertebral arteries. *Neurology (Minneap.)* **17**, 179–186.

DUFFY P. E., PORTNOY B., MAURO J. et al. (1957) Acute infantile hemiplegia secondary to spontaneous carotid thrombosis. *Neurology (Minneap.)* **7**, 664–666.

HIRSCH C. S. and ROESSMANN U. (1975) Arterial dysplasia with ruptured basilar artery aneurysm. *Hum. Pathol.* **5**, 749–758.

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A technique for the difficult peripheral arterial aneurysm

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SUMMARY

Complete external control of the vessels feeding some aneurysms may be very difficult and occasionally only achieved at the cost of damage to surrounding structures. A method is described in which Foley catheters are introduced into the feeding vessels from within the aneurysm and then cut distal to their clamped side branch to enable Dacron grafts to be passed over them and sutured in place. This technique has been used in 3 patients with very satisfactory results and is offered as an alternative when standard control is hazardous, or impossible.

SURGERY of most aneurysms is reasonably routine and follows basic principles of proximal and distal control followed by reconstitution with or without resection of the aneurysm. Most aneurysms are atherosclerotic and there is little reaction surrounding the proximal or distal vessels, making control relatively simple. In traumatic aneurysms or ruptured small vessel aneurysms, however, there is often surrounding fibrosis, haemorrhage and adjacent vital structures making the dissection more difficult. These factors may lead to extensive dissections with injury to surrounding structures.

Bole pointed out that, in a case of a false aneurysm of the abdominal aorta, a direct approach to the aortic defect through the aorta and repair from inside the lumen could avoid a tedious and often hazardous dissection around the thin-walled aneurysm or through the marked surrounding reaction (Bole et al., 1975). Robicsek et al. (1970) also described the use of a balloon catheter to obtain control in difficult abdominal aortic aneurysms.

The technique described here can be used for most traumatic aneurysms of large or small vessels, but is of particular usefulness in small vessel aneurysms where the difficulties already mentioned exist. Three cases are presented to illustrate the technique.

Case reports

Case 1: This patient was a 68-year-old man who had an indurated pulsating swelling behind his left knee. While awaiting elective surgery he developed acute pain behind the knee and was found to have ruptured the aneurysm with external haemorrhage and extensive soft tissue extravasation. Haemorrhage was controlled by local pressure but proximal control of the artery was difficult due to extravasation and was only obtained by exposure and clamping of the artery in the thigh. The distal vessels could not be found. The aneurysm was opened and bled briskly from both proximal and distal arterial orifices, coming evidently from geniculate collateral arteries. No. 10 Foley catheters were introduced into both proximal and distal arterial orifices and the cuffs inflated to control bleeding. Heparin solution was injected into the vessels via the Foley catheters which were then occluded by bulldog clamps (*Fig.* 1).

A circumferential incision was made approximately 1 mm from the orifices of the feeding and draining vessels through the wall of the aneurysm and the artery was identified as it entered and left the aneurysm. (The small cuff of aneurysm at each ostium made the anastomosis with a graft much simpler.)

Bulldog clamps were then applied to the Foley catheters near the orifice of the artery, and the catheters were divided

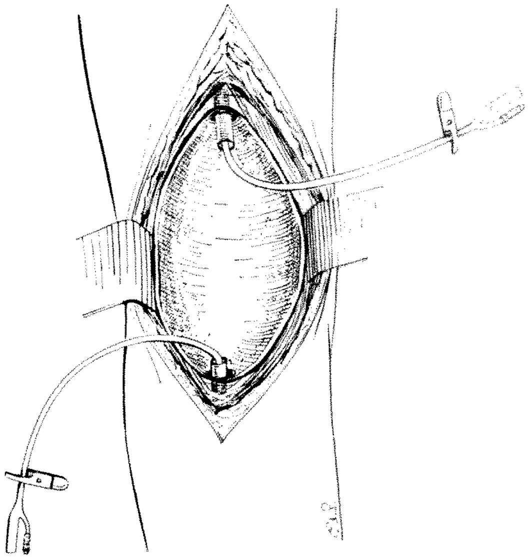

Fig. 1. The open aneurysm and proximal and distal arterial cuffs with Foley catheters inserted to effect control.

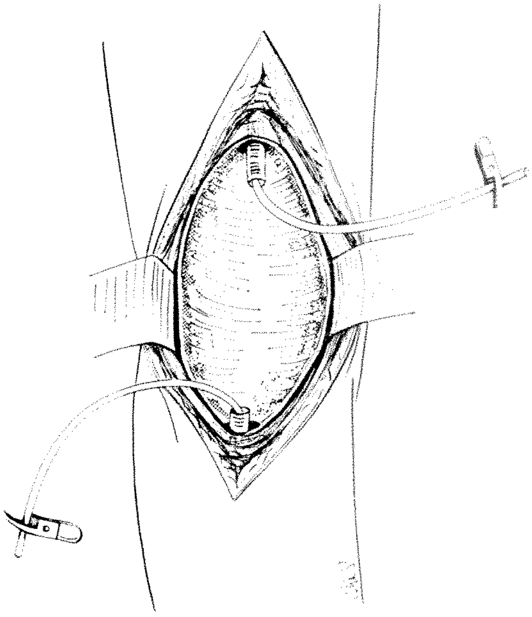

Fig. 2. The Foley catheters have been cut to allow passage of the graft. The clamps should be closer to the arterial cuff.

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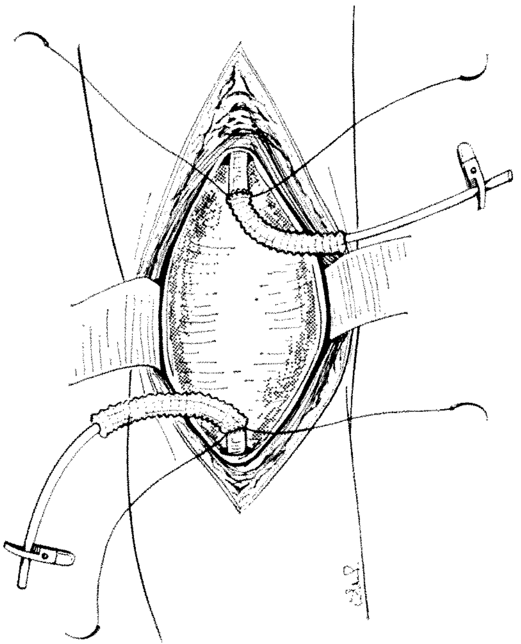

Fig. 3. The grafts, having been slipped over the free end of the catheter and the clamps applied distally, are now sutured to the arterial cuff.

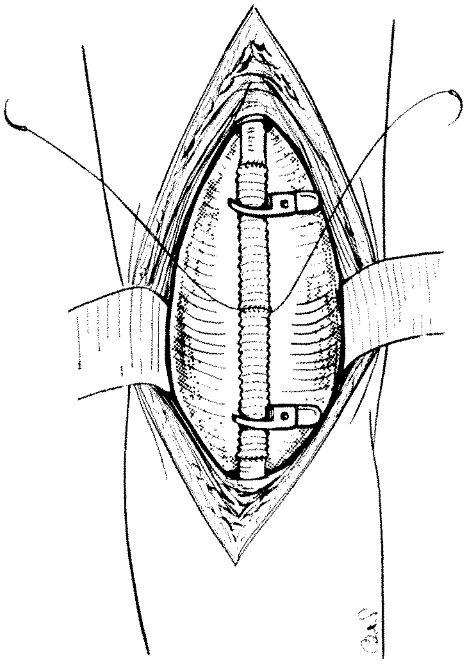

Fig. 4. Showing the completed anastomosis.

near the inlet of the bulb sideline (*Fig.* 2). Dacron grafts were then slid over the Foley catheters and a further bulldog clamp applied to the catheter as it emerged from the graft so that the previous bulldog clamp could be removed, the graft slid down to the cuff and anastomosed end to end to the artery as shown in *Fig.* 3.

The Foley catheters were then deflated and withdrawn while bulldog clamps were applied to the grafts near the anastomosis

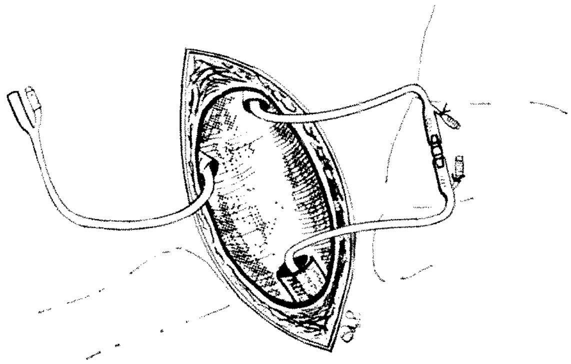

Fig. 5. As in *Case* 2, where three vessels were involved and a bypass was introduced.

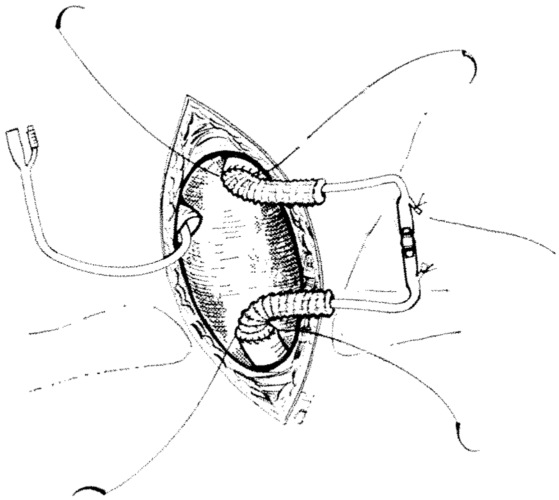

Fig. 6. The main flow anastomosis is nearing completion with bypass flow still functioning.

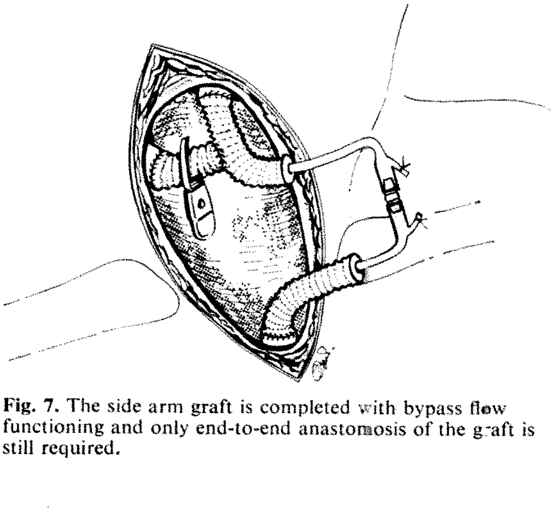

Fig. 7. The side arm graft is completed with bypass flow functioning and only end-to-end anastomosis of the graft is still required.

with the arterial cuff. The grafts were then trimmed to the desired length and sutured end to end as shown in *Fig.* 4 to complete the arterial reconstruction.

This technique is applicable to varying circumstances and can be modified to cope with the problem of more than two vital arterial orifices opening into the aneurysm.

Case 2: A young man who had been shot in the base of the neck developed a traumatic aneurysm involving the bifurcation of the innominate artery. Dissection of the aneurysm would have proved extremely difficult in view of the neighbouring brachial plexus, phrenic and vagus nerve trunks. At the same time some method of bypass to maintain carotid flow was deemed advisable. Here a modification of this technique proved of great benefit.

After control of the innominate artery via a thoracotomy incision, the aneurysm was opened and Foley catheters were introduced into the orifices of the innominate, carotid and subclavian arteries and inflated. The bulb-inflating sidelines of the innominate and carotid catheters were then tied off and the sideline excised. These two catheters were then joined with a tapered plastic connector and the bulldog clamps removed, allowing bypass flow into the carotid artery (*Fig.* 5). Circumferential dissection around the orifices of the involved arteries was a reasonably simple matter and the required grafts were then slid over the Foley catheters with temporary interruption of the bypass. Once the anastomosis of the two arteries to the two graft sections had been completed (*Fig.* 6), the bypass was again temporarily interrupted, the Foley catheters removed and the grafts trimmed and sutured end to end. This latter procedure was completed well within the accepted time for possible cerebral ischaemia. With adequate carotid flow restored, the subclavian artery orifice was dissected out and a graft sutured to it. The Foley catheter was removed, the side arm graft clamped and sutured end to side to the previously completed carotid graft.

The one point of difficulty in the second case arose from the time taken in anastomosing the subclavian graft to the carotid graft. It was realized that by altering the procedure slightly, this problem could be overcome and it is suggested that in such a case the side arm graft be anastomosed to the main graft before suturing the main graft to the arterial orifice. The Foley catheter from the side arm would be passed through the side arm graft and out of the main graft orifice with the main graft Foley catheter. The side arm graft can then be anastomosed to the side arm arterial cuff and the side arm catheter removed and a bulldog clamp applied to the side arm graft (*Fig.* 7). The two main grafts can then be sutured as previously described without any extra interruption of flow through the main graft.

Case 3: A 33-year-old man was referred to us 14 days after being stabbed above the right clavicle. He presented with an enlarging pulsatile swelling in the posterior triangle. There was some neurological deficit involving C5 and C6. No bruit was audible and arteriography showed an aneurysmal dilatation of the right subclavian/axillary artery just lateral to the first rib.

The aneurysm was approached via a supraclavicular incision and the feeding vessel controlled by digital pressure. The aneurysm was opened and backflow from the distal orifice initially stopped by direct pressure. Foley catheters were introduced into both orifices and the bulbs inflated with complete control of bleeding. In this case there was still a posterior wall of artery intact and the cuff was so dissected out to allow end-to-end reconstitution of the artery without the use of a graft. Prolene sutures were inserted with the Foley catheters in place and the catheters removed to allow the final closure of the anastomosis while digital control of the feeding vessel was applied.

Discussion

Although the treatment of traumatic or ruptured peripheral arterial aneurysms may be relatively straightforward, it often involves prolonged and tedious dissection to obtain control of the feeding and draining vessels. Especially in the carotid, subclavian, axillary and inguinal areas, where many of these traumatic aneurysms occur, the neighbouring vital structures can easily be damaged, resulting in permanent loss of function, and some method which would obviate this hazard would be very helpful.

It is obviously desirable that some form of proximal control should be achieved when possible in aneurysms where loss of control due to failure of the catheter would be catastrophic, e.g. control of the innominate artery in *Case* 2. Some surgeons are prepared to operate on the carotid artery without a bypass provided that angiography has shown adequate cross flow from the opposite side. There still remains, however, a small percentage of patients who develop cerebral ischaemia on occlusion of the carotid. In Rittenhouse's review it was stated that 24 per cent of patients who had occlusion of the carotid artery developed a neurological complication (Ritterhouse et al., 1972). Arpin et al. (1975) pointed out that extracranial carotid aneurysms of any aetiology were very rare, but when they do occur, they can result in tragic consequences if the patient should develop cerebral iscahemia during the operative procedures. Some form of bypass should make such operations safer provided that, as in the method here described, it is simple and not likely to cause complications in itself.

It is suggested that this method will be found to be applicable in varied circumstances and that where standard methods may prove hazardous, this technique could result in safer and quicker operations.

References

ARPIN E. J. and DOWNS A. R. (1975) Two false aneurysms of the common carotid artery—a delayed complication of penetrating cervical trauma. *J. Trauma* **15**, 976–980.

BOLE P. V., CORTES L. E., MUNDA R. Y., DEVANESAN J. and PURDY R. T. (1975) Repair of a false aneurysm of the abdominal aorta. *J. Trauma* **15**, 255–259.

RITTENHOUSE E. A., RADK H. M. and SUMMER D. S. (1972) Carotid artery aneurysms. *Arch. Surg.* **105**, 786–789.

ROBICSEK F., DAUGHERTY H. K. and MULLEN D. (1970) The elective use of balloon obstruction in aortic surgery. *Surgery* **68**, 774–777.

Paper accepted 20 April 1979.

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Noxythiolin (Noxyflex), aprotinin (Trasylol) and peritoneal adhesion formation: an experimental study in the rat

A. T. RAFTERY*

SUMMARY

Clinical and experimental studies have suggested that noxythiolin and aprotinin may prevent intraperitoneal adhesion formation. A comparison was therefore made of their efficacy in preventing the reformation of adhesions following surgical lysis in a controlled trial using rats. Neither noxythiolon nor aprotinin had any significant benefit over surgical lysis alone. The mortality rate was high in the noxythiolin-treated group.

INTRAPERITONEAL adhesions are a common cause of intestinal obstruction (Ellis, 1974). Numerous methods have been tried over the years in an attempt to prevent adhesions, but with little success, despite initial enthusiastic reports. Recently, two further substances have been reported as efficacious in decreasing the incidence of intraperitoneal adhesions, namely noxythiolin (Noxyflex, Geistlich) and aprotinin (Trasylol, Bayer). Following the observation of Tolhurst Cleaver et al. (1974) that adhesions occurred less frequently in rats given intraperitoneal lavage with noxythiolin than those given lavage with Hartmann's solution, Gilmore and Reid (1976) showed that a single intraperitoneal dose of noxythiolin reduced the incidence of adhesions in rats. Experimental studies (Vorster, 1968; Grundmann, 1969) have shown that aprotinin reduces the incidence of adhesions and Mooney (1976) has shown a reduced incidence of adhesions in a clinical study. However, these studies all relate to prevention of adhesions at an initial laparotomy. As Ellis (1971) has pointed out, the vast majority of adhesions are harmless and may well be protective or even life-saving to the patient, for example in protecting an anastomotic line in which the blood supply was endangered or in localizing infection. In the study reported here no attempt was made to prevent adhesions forming following the initial laparotomy, but, following a second laparotomy to divide the adhesions created at the initial laparotomy, either noxythiolin or aprotinin was instilled into the peritoneal cavity in order to assess the efficacy of these substances at preventing the reformation of adhesions.

Materials and methods

Adult male Sprague-Dawley rats weighing 250-300 g were used in this investigation. Anaesthesia was induced with ether and maintained with a nitrous oxide, halothane and oxygen mixture. At the initial laparotomy the abdomen was opened through a midline incision 5 cm long. Adhesions were created by a method of multiple peritoneal trauma. The operative techniques were as follows.

A defect 2 cm × 0·5 cm was made in the left flank, involving removal of the peritoneum and underlying layer of muscle within this area. The defect was repaired with a continuous 3/0 chromic catgut suture. A similar defect was made on the right flank, but this was not sutured. The caecum was delivered from the wound and its surface rubbed briskly with sterile gauze until petechial haemorrhages were observed. The peritoneum at the ileocaecal junction was grasped between forceps and stripped off the antimesenteric border of the ileum for about 5 cm from the ileocaecal junction (Glucksman, 1966), removing a strip of peritoneum about 1 mm wide and also the underlying layer of longitudinal muscle. The abdominal incision was closed in two layers, catgut sutures being placed through the musculoperitoneal layers and silk sutures through the skin.

The rats were subjected to a second laparotomy 2 weeks later. The position of all adhesions was noted and the adhesions divided with scissors. At the end of this procedure, just prior to closure of the abdomen, 2·5 ml of one of a batch of numbered solutions (1–100) was instilled into the peritoneal cavity. Surviving animals were killed 2 weeks later and inspected for adhesions. The position of all adhesions was noted. At completion of the experiment the number code of the solutions was broken. In total, 120 animals were operated on and 100 received an intraperitoneal solution at the completion of the second laparotomy. The following solutions were instilled into the peritoneal cavity: 20 rats received 2·5 ml of normal saline, 20 received 2·5 ml of 2·5 per cent Noxyflex (noxythiolin + amethocaine), 20 received 2·5 ml of 2·5 per cent Noxyflex S (noxythiolin alone), 20 received 25 000 units of aprotinin and 20 received 50 000 units of aprotinin. Statistical analysis of the results was carried out using Fisher's exact test.

Results

Some adhesions formed in each animal following the initial laparotomy. As each group of animals acted as their own 'controls' in assessing the results of the various treatments, statistical analysis was carried out to assess whether there was any significant difference between the number of adhesions in each control group prior to treatment. None was found.

The sites of adhesion formation and the number of animals having adhesions at the various sites are shown in *Tables I–VI*. Following the second laparotomy there was a significantly increased mortality in the group treated with Noxyflex ($P<0{\cdot}001$) and also in the group treated with Noxyflex S ($P<0{\cdot}005$). None of the treatment groups showed a significant reduction in adhesions compared with surgical lysis alone. On the contrary, there was a significant increase in adhesions to the left flank in the group treated with Noxyflex S ($P<0{\cdot}005$). It was not possible to evaluate statistically the effect of Noxyflex on adhesions due to the high mortality in this group. Post-mortem examination of the 2 rats that died in the saline-treated group showed that death occurred from peritonitis resulting from caecal volvulus and gangrene of the caecum. All the rats that died in the groups treated with Noxyflex and Noxyflex S did so within 48 h of operation. Limited post-mortem examination revealed no abnormality in the peritoneal cavity, but showed bilateral pleural effusions and haemorrhagic lesions in the lungs.

Discussion

The results show that none of the substances used in an attempt to prevent adhesions has a clear advantage

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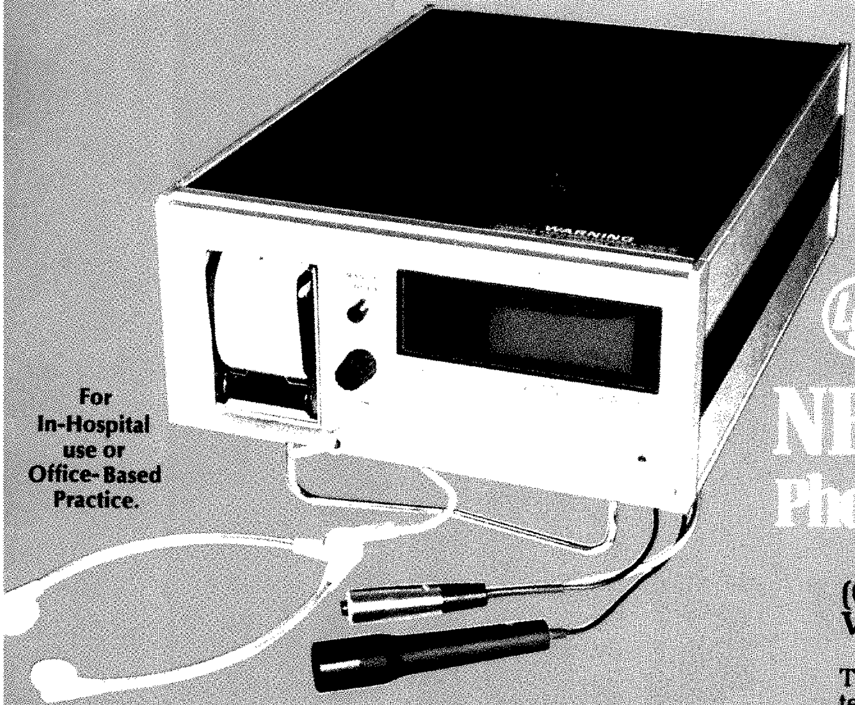

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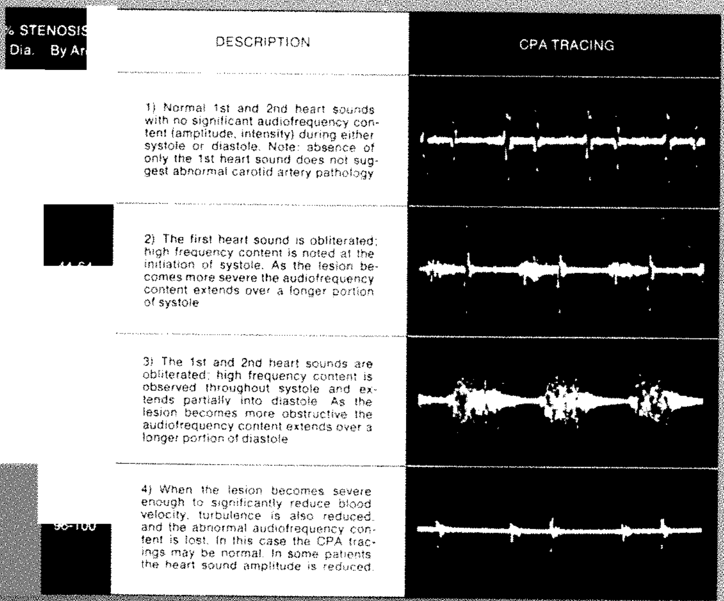
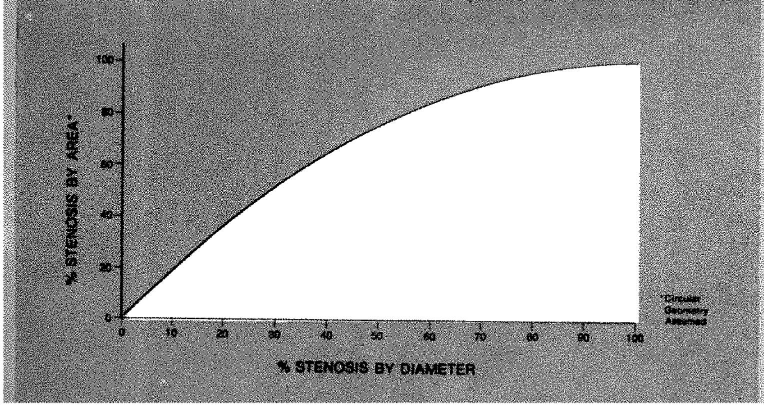


% STENOSIS Dia. By Ar	DESCRIPTION	CPA TRACING
	1) Normal 1st and 2nd heart sounds with no significant audiofrequency content (amplitude, intensity) during either systole or diastole. Note: absence of only the 1st heart sound does not suggest abnormal carotid artery pathology	
	2) The first heart sound is obliterated; high frequency content is noted at the initiation of systole. As the lesion becomes more severe the audiofrequency content extends over a longer portion of systole	
	3) The 1st and 2nd heart sounds are obliterated; high frequency content is observed throughout systole and extends partially into diastole. As the lesion becomes more obstructive the audiofrequency content extends over a longer portion of diastole	
	4) When the lesion becomes severe enough to significantly reduce blood velocity, turbulence is also reduced, and the abnormal audiofrequency content is lost. In this case the CPA tracings may be normal. In some patients the heart sound amplitude is reduced.	



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over surgical lysis alone. Ideally, any substance tested should totally prevent adhesions. Reduction in the number of adhesions or their length of attachment is probably not significant since it is apparent from clinical experience that a single band adhesion can be just as troublesome in terms of intestinal obstruction and strangulation as numerous smaller adhesions.

The experimental model was deliberately designed so that no attempt was made to prevent adhesions at the initial laparotomy. As Ellis (1971) has stated, adhesions are vascular grafts to areas of doubtful viability and it is uncertain whether we should aim to prevent adhesions after a first laparotomy. Where we should aim to prevent adhesions is in the patient undergoing a second or subsequent laparotomy for intestinal obstruction due to adhesions where the bowel is viable and where, after dividing the adhesions, we seek to prevent them reforming.

Sutured peritoneal defects have been shown to act as an adhesive stimulus (Ellis, 1962; Gilmore and Reid, 1976), but in this study adhesions formed to the defect in only about one-third of animals compared with all animals as reported by Gilmore and Reid (1976). This may relate to the fact that the defect was sutured with catgut rather than silk as in the study of Gilmore and Reid (1976). It should, however, be noted that more adhesions formed to the sutured defect in the left flank than to the unsutured defect in the right flank following the initial laparotomy, thus confirming the work of Ellis (1962) who showed that sutured peritoneal defects acted as a stimulus to adhesion formation. Also, in contrast to Gilmore and Reid's study (1976), no reduction in adhesion formation was found with noxythiolin and also the mortality rate was high.

Noxythiolin is manufactured in two forms: Noxyflex which contains 10 mg of amethocaine in each 2·5 g of noxythiolin and Noxyflex S which contains no amethocaine. After breaking the code it was found that all except one animal in the Noxyflex group died and also 8 of those in the Noxyflex S group. Tolhurst Cleaver et al. (1974) reported 100 per cent mortality in a group of rats with faecal peritonitis treated with Noxyflex. No satisfactory explanation could be found for this at the time, but recently it has become apparent that the amethocaine contained in Noxyflex may be toxic to rats. The convulsant dose given intravenously to rats is 1·5 mg/kg body weight (Edwards, 1978). The volume of solution given to the rats, i.e. 2·5 ml, contains 0·25 mg, giving a dose of approximately 1 mg/kg given intraperitoneally. Further ether may raise the toxicity of amethocaine up to tenfold and ether was used to induce anaesthesia and therefore could have taken the dose of amethocaine past the convulsant dose to the lethal dose. Although this provides a satisfactory explanation for those animals treated with Noxyflex, it does not explain the 40 per cent mortality in the animals treated with Noxyflex S which does not contain amethocaine. It must therefore be assumed that noxythiolin in the concentration used is absorbed rapidly through the large areas of peritoneal defect and is toxic to rats. The discrepancy between these results and those of Gilmore and Reid (1976) who had no mortality may be due to the fact that they used a sutured wound only to stimulate adhesions and there were no large raw areas of peritoneum such as those

Table I: SURGICAL LYSIS ALONE

Site of adhesion	No. animals with adhesions Initial laparotomy ($n = 20$)	 After lysis ($n = 20$)
Right flank	1	1
Left flank	10	0
Caecum	20	14
Ileum	18	15

Deaths = 0; % survivors having adhesions = 90.

Table II: SURGICAL LYSIS PLUS SALINE

Site of adhesion	No. animals with adhesions Initial laparotomy ($n = 20$)	 After lysis + saline ($n = 18$)
Right flank	0	0
Left flank	6	2
Caecum	18	16
Ileum	17	16

Deaths = 2; % survivors having adhesions = 100.

Table III: SURGICAL LYSIS PLUS NOXYFLEX (2·5 PER CENT)

Site of adhesion	No. animals with adhesions Initial laparotomy ($n = 20$)	 After lysis + Noxyflex ($n = 1$)
Right flank	0	0
Left flank	6	0
Caecum	17	1
Ileum	16	1

Deaths = 19; % survivors having adhesions = 100.

Table IV: SURGICAL LYSIS PLUS NOXYFLEX S (2·5 PER CENT)

Site of adhesion	No. animals with adhesions Initial laparotomy ($n = 20$)	 After lysis + Noxyflex S ($n = 12$)
Right flank	2	2
Left flank	10	6
Caecum	15	12
Ileum	16	12

Deaths = 8; % survivors having adhesions = 100.

Table V: SURGICAL LYSIS PLUS TRASYLOL (25 000 UNITS)

Site of adhesion	No. animals with adhesions Initial laparotomy ($n = 20$)	 After lysis + Trasylol ($n = 20$)
Right flank	1	0
Left flank	7	1
Caecum	19	15
Ileum	17	16

Deaths = 0; % survivors having adhesions = 85.

Table VI: SURGICAL LYSIS PLUS TRASYLOL (50 000 UNITS)

Site of adhesion	No. animals with adhesions Initial laparotomy ($n = 20$)	 After lysis + Trasylol ($n = 20$)
Right flank	0	0
Left flank	6	4
Caecum	20	18
Ileum	20	18

Deaths = 0; % survivors having adhesions = 100.

in the present study through which noxythiolin may be rapidly absorbed. Also Gilmore and Reid (1976) used only 1 per cent noxythiolin, compared with 2·5 per cent in the present study.

Animals treated with aprotinin showed no reduction in adhesion formation compared with surgical lysis alone. This does not support the work of Vorster (1968) and Grundmann (1969) who showed that adhesions produced by peritoneal abrasion and instillation of talc could be reduced by a single intraperitoneal injection of aprotinin. However, it should be noted that in these studies adhesions were not completely abolished (Vorster, 1968), but their area of attachment was reduced (Grundmann, 1969). Certainly there are good theoretical reasons for believing that aprotinin should reduce adhesions since it has been shown to reduce the inflammatory response in peritoneal wounds created by cautery and to 'prevent the development of inflammatory granulation tissue' (Grundmann, 1969). Two recent clinical papers have also suggested that aprotinin reduces adhesions. Mooney (1976) treated 20 patients with intraperitoneal aprotinin and at a 'second look' procedure, i.e. laparotomy or laparoscopy, there was a 'marked reduction' in adhesions in 16 of the patients. However, this was an uncontrolled trial. More recently, Perovic et al. (1978) have compared a single dose of intraperitoneal aprotinin with no such treatment in perforated appendicitis in children. The presence of adhesions was indirectly assessed by comparing the incidence of 'mechanical ileus' in the two groups. It was significantly higher in the untreated group. However, the absence of 'mechanical ileus' does not necessarily prove absence of intraperitoneal adhesions.

The results obtained in the experimental model certainly do not support the claims that a single intraperitoneal dose of either noxythiolin or aprotinin prevents adhesions.

Acknowledgements

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References

EDWARDS K. G. (1978) Personal communication.

ELLIS H. (1962) The aetiology of postoperative abdominal adhesions. An experimental study. *Br. J. Surg.* **50**, 10–16.

ELLIS H. (1971) The cause and prevention of post-operative intraperitoneal adhesions. *Surg. Gynecol. Obstet.* **133**, 497–511.

ELLIS H. (1974) Intraperitoneal adhesions. *Br. J. Hosp. Med.* **11**, 401–408.

GILMORE O. J. A. and REID C. (1976) Noxythiolin and peritoneal adhesion formation. *Br. J. Surg.* **63**, 978–980.

GLUCKSMAN D. (1966) Serosal integrity and intestinal adhesions. *Surgery* **60**, 1009–1011.

GRUNDMANN E. (1969) On the use of proteinase inhibitor Trasylol as an abdominal-antiadhesion prophylactic. In: HABERLAND G. L., HUBER P. and MATIS P. (ed.) *New Aspects of Trasylol Therapy*. Stuttgart, Schattauer, vol. 4, pp. 65–77.

MOONEY R. A. H. (1976) Prevention of peritoneal adhesions with aprotinin (Trasylol). *J. Int. Med. Res.* **4**, 360–363.

PEROVIC S., MAKSIMOVIC L. J., DJAJA M. et al. (1978) Prophylaxis of adhesions with Trasylol in cases of perforated appendicitis in children. *J. Int. Med. Res.* **6**, 89–93.

TOLHURST CLEAVER C. L., HOPKINS A. D., KEE KWONG K. C. N. G. et al. (1974) The effect of postoperative peritoneal lavage on survival peritoneal wound healing and adhesion formation following faecal peritonitis: an experimental study in the rat. *Br. J. Surg.* **61**, 601–604.

VORSTER C. F. (1968) Prophylaxis of adhesions by means of proteinase inhibitors. In: MARX R., IMDAHL H. and HABERLAND G. L. (ed.). *New Aspects of Trasylol Therapy*. Stuttgart, Schattauer, vol. 2, pp. 151–159.

Paper accepted 7 February 1979.

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A safe and effective disposable low pressure suction drain

M. F. SEELY, W. A. HYDE AND MILES IRVING*

SUMMARY

The physical and microbiological properties of a new disposable suction drainage system have been investigated under clinical and laboratory conditions. The system appears to have overcome the disadvantages associated with previous disposable and reusable low pressure suction drainage systems for use after surgical operation in that this system effectively prevents reflux and retrograde contamination.

SUCTION drainage systems are widely used in surgical practice to remove blood and secretions that might otherwise lead to haematoma or seroma formation with possible infection and delay in healing. Such drains may be left in position for several days, their effectiveness being maintained by repeated charging of the vacuum.

We have examined the physical and microbiological properties of a disposable system (DreVac Drain, Astra-Sjuco AB, Sweden) which claims to have incorporated mechanisms that effectively prevent the danger of retrograde contamination during the maintenance of suction and whilst recharging is taking place to see if the claims can be substantiated.

The Drevac system

The system (*Fig.* 1) consists of a fine plastic cannula with multiple perforations at one end which is laid into the site to be drained, the other end attached to a trocar being brought to the exterior through the body wall. The cannula is attached to the inlet tube of the bellows. The tube can be occluded by a clamp to isolate the bellows during recharging. The inlet tube within the bellows is protected by a plastic flap valve which prevents reflux during charging (*Fig.* 2). An outlet tube from the bellows, which can also be occluded by a clamp, leads into a plastic drainage bag where it is similarly protected by a flap valve to prevent reflux. The air outlet from the drainage bag is protected by a synthetic foam plug.

Charging of the system is accomplished by occluding the inlet tube, opening the outlet clamp and squeezing the bellows, following which the outlet clamp is closed and the inlet clamp opened. The bellows are rather difficult to compress and never empty completely, but this does not interfere with effective functioning.

Studies

Loss of vacuum

The loss of vacuum over a period of 12 h in the completely sealed bellows was studied in eight systems by connecting the inlet tube of the bellows to a manometer consisting of a glass tube standing in a conical flask containing mercury. The bellows were then evacuated and the column height obtained was measured at zero time and every 30 min for the first hour and then hourly thereafter to the end of the 12 h period. The study was repeated 5 days later after eleven rechargings to see whether the initial physical properties had changed.

Reflux from the bellows into the inlet tube was studied in eight systems by sucking up water into the bellows and then trying to evacuate the bellows manually with the outlet tube clamped and the inlet tube unclamped. The water contained methylene blue for easy visualization of any reflux.

Bacteriological studies

Four bacteriological studies of the system were undertaken.

1. Whole systems were removed from 33 patients in whom they had been used and the bacteriological state of the suction catheter, the bellows and the drainage bag were all determined. Particular note was made of whether bacteria present in the drainage bag could be grown from the bellows and catheter.
2. Six systems were set up in the surgical wards with the drainage cannulas inserted through the rubber diaphragm of a sterile glass blood bottle containing a clear culture medium (thioglycollate USP haemin and menadione LAB-M). The system was repeatedly charged at 12-hourly intervals over a 5-day period, on each occasion the bellows being allowed to suck in 30 ml of culture medium. Three of the systems were then isolated by occluding the inlet clip and three were left without suction throughout the study. To allow easy suction of the system a no. 17 BWG needle with a 13-mm Millipore 0·23 μm bacterial filter was inserted through the diaphragm to allow equalization of pressure.
3. As the only possible point of outside contamination of the system is through the air filter in the drainage bag, the study was repeated with constant moistening of the air filter with the culture medium such as might occur if a patient compressed the bag by lying on it.
4. Experiment 3 above was repeated in the laboratory, but on this occasion the air filter into the drainage bag was fitted with a 0·23 μm Millipore filter. The drainage bags were then contaminated with *Pseudomonas aeruginosa* and the system then studied in the same way for a further 5 days.

All specimens from the above experiments were collected in a laminar flow filtered exhaust station, the drains being swabbed with 70 per cent isopropyl alcohol before the contents were withdrawn with sterile syringes and cultured aerobically and anaerobically.

Bacterial growth was classified depending upon the number of colonies:

$>300\times10^2$/ml	+++
$>150<300\times10^2$/ml	++
$>50<150\times10^2$/ml	+
$1<50\times10^2$/ml	±

Organisms were identified by conventional laboratory methods.

Results

Loss of vacuum

The loss of vacuum in the bellows after occlusion of the inlet tube is shown in *Fig.* 3. An initial rapid fall-off in suction pressure of 20 mmHg in the first hour is followed by a period of stabilization over the next 11 h to a level between 100 and 110 mmHg. After 5 days and eleven evacuations the maximum vacuum that could be obtained was only some 10 mmHg less than that obtainable on the first day, and at 12 h the vacuum measured was no different from that on the first day.

Reflux

In none of the eight systems tested could reflux up the unoccluded inlet tube be obtained by compression of the bellows.

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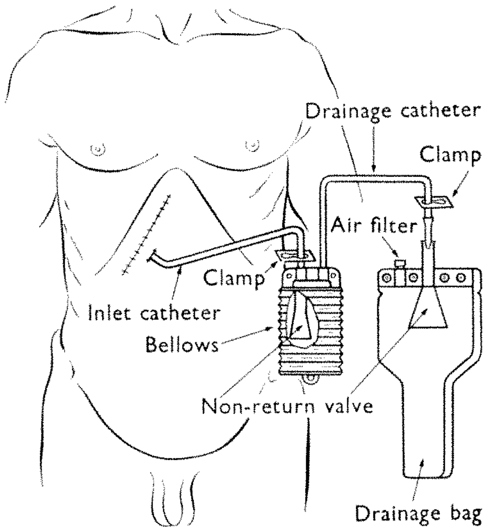

Fig. 1. DreVac suction drainage system.

Table I: ORGANISMS GROWN FROM THE 7 CONTAMINATED DRAINAGE SYSTEMS USED IN PATIENTS

Drain no.	Colony growth in aerobic Columbia blood agar		
	Inlet tube	Bellows	Drainage bag
4	No growth	No growth	*Str. faecalis* + + +
7*	*Ent. aerogenes* + + +	*Ent. aerogenes* + + +	*Ent. aerogenes* + + + *Str. faecalis* + + +
9†	*E. coli* + + + β-haem. str. ± group B	*E. coli* + + + β-haem. str. ± group B	*E. coli* + + + β-haem. str. + group B
10‡	*E. coli* + + +	*E. coli* + + +	*E. coli* + + +
12*	*Ent. aerogenes* + + +	*Ent. aerogenes* + + +	*Ent. aerogenes* + + +
13‡	*E. coli* + + +	*E. coli* + + +	*E. coli* + + +
22	No growth	No growth	*Staph. albus* + + Diphtheroids +

Ent., *Enterobacter; E.*, *Escherichia;* β-haem. str. β-haemolytic streptococcus: *Staph.*, *Staphylococcus.*
* Patients with bile peritonitis.
† Patient with tubo-ovarian abscess.
‡ Patients with abscesses associated with Crohn's disease.
For explanation of colony growth *see* text.

Bacteriological studies

Organisms were isolated from 7 of the 33 systems removed from patients. Bacteria were present in all three compartments of 5 of the systems studied which had all come from patients with intraperitoneal infections. From 1 of these 5 systems, and from the other 2 systems, organisms were isolated from the drainage bags which could not be isolated from either the bellows or inlet in spite of enrichment techniques (*Table I*). These were presumed to be environmental contaminants.

Six of the 33 systems investigated were found to have had their air filters accidentally moistened by the contents of the drainage bags. The three instances of contamination in the drainage bags came from this group.

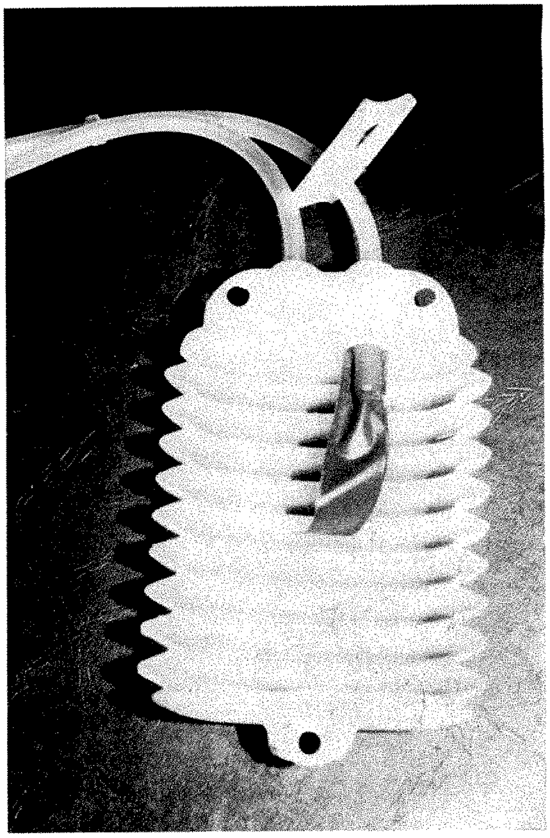

Fig. 2. View of non-return valve in the cut-open bellows.

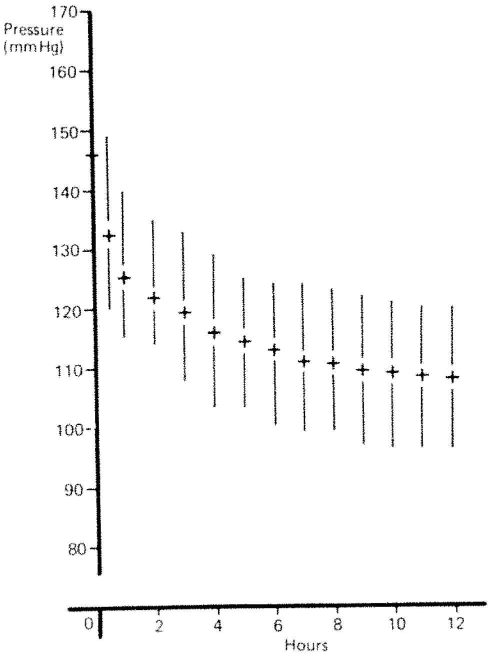

Fig. 3. Loss of vacuum in the bellows measured over a period of 12 h in eight systems (mean ± s.d.).

The experiments conducted in the ward showed that the whole system remained sterile in the wards provided that the drainage bag inlet filter was not contaminated. Of the 6 systems where the inlet filter was deliberately moistened with culture medium, 4 showed contamination of the culture medium in the drainage bags by the fifth day with three species of organism. However, in no instance did retrograde contamination from the drainage bags to the bellows or reservoir occur.

In the studies in which the drainage bag was contaminated with pseudomonas no spread to the bellows or reservoir occurred throughout the 5 days.

Discussion

The main concern always expressed about surgical drains has been the danger of migration of microorganisms by retrograde spread down into the cavities being drained. In the case of suction drainage systems these fears are compounded by the possibility of reflux into the drained area during recharging or accidental compression of the container. It was such an occurrence that according to Wyatt (1969) led to two severe wound infections following cholecystectomy and prostatectomy.

A detailed study of disposable and reusable drainage systems by Lumley et al. (1974) showed that both types were subject to spontaneous loss of vacuum and that positional change of the container of the magnitude encountered in clinical practice could esaily produce reversal of flow from the container into the wound.

Their study also showed that in laboratory conditions designed to simulate the clinical situation, bacterial contamination could occur in both systems, but was more likely in the disposable rather than the reusable systems.

The main requirements of an effective low pressure suction drainage system should be maintenance of suction without the need for frequent recharging and the incorporation of mechanisms that effectively prevent reflux and retrograde bacterial contamination.

The DreVac system would appear on the basis of our investigations to have achieved this aim. Its ability to maintain low pressure suction after repeated compression over several days compares favourably with the other disposable systems described by Lumley et al. (1974). The risk of reflux and retrograde contamination even by an organism such as *Pseudomonas aeruginosa*, which is motile at room temperature, appears to have been eliminated by the use of the flap valve and occlusive clips reinforced by the fact that the whole system is a closed one. Indeed, even when contamination of the drainage bags occurred either unintentionally or deliberately, as in the laboratory studies, no retrograde contamination of the bellows or culture medium reservoir could be detected. Our studies demonstrate that even contamination of the drainage bag can be prevented by the fitting of a Millipore filter to the air inlet.

Some authorities have counselled against the use of drainage after splenectomy because of the danger of subphrenic abscess formation. We have used this system in over 70 splenectomies in the past 3 years without complication.

It would appear that, apart from some difficulty in physically compressing the bellows, the DreVac disposable drain satisfies the mechanical and bacteriological properties necessary for a safe, effective low pressure suction drainage system.

References

LUMLEY J. S. P., BRITTON B. J. and CHATTOPADHYAY B. (1974) The physical and bacteriological properties of disposable and non-disposable suction drainage units in the laboratory. *Br. J. Surg.* **61**, 832–837.

WYATT A. P. (1969) Hazard of vacu-drain system. *Lancet* 2, 1132.

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Br. J. Surg. Vol. 66 (1979) 660–662

Duct ectasia in the male

R. E. MANSEL AND W. P. MORGAN*

SUMMARY

Three cases of inflammatory duct ectasia occurring in the male breast are described. The clinical presentation of the disease in the male closely resembles that in the female. Nipple retraction, nipple discharge, periareolar inflammation and bilateral involvement are all seen. Conservative measures produced unsatisfactory results similar to those in women. A similar operative approach to that used in women is advocated.

INGIER (1909) first drew attention to the association of inflammation with mammary duct ectasia and his findings have been confirmed by several authors (Adair, 1933; Bonser et al., 1961; Walker and Sandison, 1964; Haagensen, 1971). None of these authors has reported a similar condition in the male breast, although the histological picture of periductal mastitis has been described in a male by Tedeschi and McCarthy (1974).

Case reports

Case 1: J. C., aged 62 years, presented in October 1976 with a 4-week history of a painful red lump in the left breast associated with an intermittent bloody nipple discharge. He had noticed increasing bilateral painless nipple retraction over the previous 2 years. His past history included a transurethral prostatectomy one year previously for benign hypertrophy and neurological investigation in 1970 for recurrent headaches. Air encephalography showed slightly dilated lateral ventricles and a diagnosis of arrested hydrocephalus was made.

Examination in October 1976 showed a 5 × 5 cm red, tender, non-fluctuant mass lying deep to the left areola. Both nipples were deeply retracted. Mammograms were reported as showing bilateral gynaecomastia, greater on the left side. The redness and tenderness disappeared spontaneously over the next 2 weeks, but the inflammation returned 1 month later and in December 1976 the patient was admitted for drainage of an abscess in the left breast. The pus gave a growth of *Staphylococcus aureus* and *Staphylococcus albus* on culture. The wound healed after several days' drainage, but the inflammatory process recurred 2 weeks later. The breast was now diffusely indurated and oedematous and a central mass 3·5 × 3 cm was palpable beneath the partially retracted nipple (*Fig*. 1).

At operation the left breast and terminal lactiferous ducts were removed by an extended total ductal excision operation as developed by Urban and Adair (Hadfield, 1960) and the wound was packed with acroflavine gauze. Histology showed extensive chronic inflammation and fibrosis with granulation tissue (*Fig*. 2). The wound was dressed with a silicone elastomer stent (Wood et al., 1977) and healed up over the next month.

The patient remained well for the next 5 months but in June 1977 he again presented as an emergency with a 4-day history of pain in the other breast. On examination he was found to have a subareolar abscess in the right breast and this was drained under general anaesthetic. *Bacteroides fragilis* was subsequently cultured from the pus obtained. The wound healed over the next month but pain and induration persisted under the areola and total ductal excision was carried out in September 1977 using a subareolar incision. The breast tissue, which mainly consisted of dense fibrotic bands, was completely removed after freeing the lactiferous ducts from the base of the nipple. This procedure allowed the retracted nipple to evert normally and the wound was closed with suction drainage. Histological examination of the specimen showed chronic stromal inflammation and a mild degree of ductal proliferation which was accompanied by periductal inflammation. A wound swab taken at operation grew *S. albus*, *S. aureus* and a non-haemolytic streptococcus. The wound healed uneventfully (*Fig*. 3). The patient has had no further trouble on either side.

Case 2: J. L., aged 47 years, presented in June 1973 with a 12-year history of recurrent abscesses in the right breast. On previous occasions the abscess had discharged spontaneously through a small periareolar sinus. There was no history of diabetes mellitus. On examination a small abscess was noted beneath the right nipple which appeared to be otherwise normal. The abscess was incised and packed after evacuating some thick pus, which was sterile on culture. The wound healed satisfactorily and the patient was discharged from the out-patient clinic. However, he was admitted again as an emergency in February 1976 with a recurrent abscess draining through a small sinus on the medial edge of the areola. The patient reported that abscess formation had occurred two or three times since the first operation. Incision drainage and packing were again carried out with evacuation of thick pus which grew *Escherichia coli*. The patient was discharged with a healed wound in March 1976.

Eleven months later he was referred to outpatients with a recurrence of the discharging sinus medial to the right nipple, but without abscess formation. At operation in March 1977 the sinus and a block of underlying breast tissue were excised with primary wound closure under antibiotic cover. Histological examination showed large areas of chronic inflammation with marked focal granulomatous reaction. The wound healed satisfactorily and the patient was discharged, only to reappear in 8 months time with another sinus medial to the right nipple. At this stage it was felt that a radical excision was necessary to clear all diseased tissue. The patient expressed a preference for the certainty of a conservative simple mastectomy to a ductal excision procedure and this was carried out in November 1977. Postoperative healing was uneventful and the patient has remained free of inflammation since the operation.

Case 3: W. G., aged 52 years, presented in April 1978 with an 8-week history of a tender lump in the left breast. This had been treated with antibiotics by his family practitioner. He had then spontaneously developed an intermittent discharge from a sinus situated at 9 o'clock on the left areolar margin (*Fig*. 4). There were no associated problems apart from chronic bronchitis (he smoked 99 g of tobacco per week) and the patient had been taking no other medication. Culture of the discharge was sterile.

At operation 2 weeks later a probe could be passed through the sinus and it ran under the areola to the nipple. It was possible to carry out a subcutaneous mastectomy with excision of the terminal ducts through a circumareolar incision. This included all the tissue surrounding the probe. The wound was closed primarily with sutures and suction drainage. The patient made an uneventful postoperative recovery.

Histology of the excised specimen showed the skin surrounding the fistulous opening to have dense fibrous tissue in the dermis with granulation tissue, containing a mixture of chronic inflammatory and occasional multinucleate giant cells. No acid-fast bacilli were seen. The excised breast tissue contained only one rather distorted duct.

Discussion

Female mammary duct ectasia with associated periductal mastitis, juxta-areola abscess formation and, in a proportion of cases, fistula formation is a

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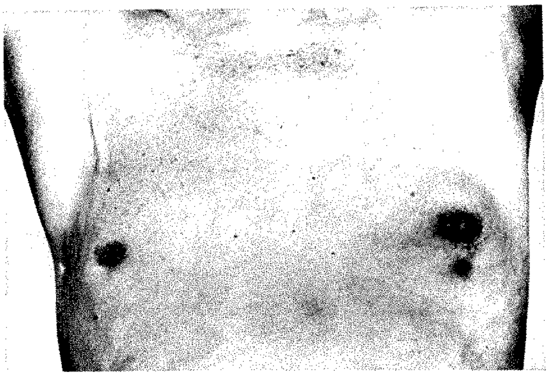

Fig. 1. *Case* 1. Showing an inflammatory mass deep to the left nipple. Note the retracted right nipple.

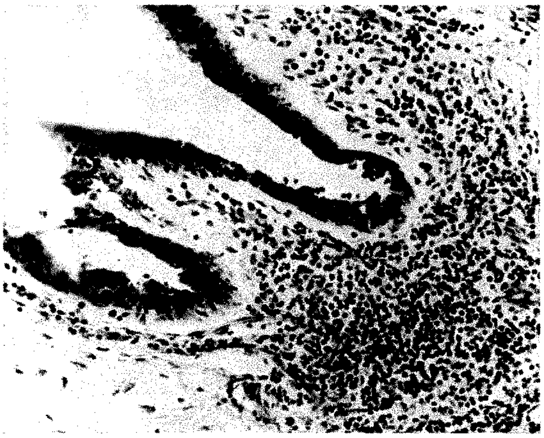

Fig. 2. *Case* 1. Histological section demonstrating chronic inflammatory infiltrate surrounding the breast duct. (HE. × 16.)

well-documented condition (Haagensen, 1971; Walker and Sandison, 1964).

Walker and Sandison have described four clinical types of presentation of duct ectasia in the female:

1. Nipple discharge from a clinically normal breast.
2. A soft irregular mass with an indefinite edge, present in or near the subareolar region.
3. A tender inflamed lump in the juxta-areolar area leading to sterile abscess formation. A simple incision leads to super-added infection with recurrent abscess and fistula formation.
4. A variably tender, craggy, hard mass with irregular edges, sometimes attached to skin and of recent onset.

All three of our male cases presented with juxta-areolar abscess formation, as in Walker and Sandison's group 3. In two of the male cases, simple incision and drainage led to repeated abscess and fistula formation. In the third case, the fistula appeared spontaneously. Other features seen in the male cases which are also seen in the female are the occurrence of bilateral disease, nipple discharge and nipple retraction. Our cases again mirrored the finding in females that pus is commonly sterile in the early stage of the disease but may be invaded with a variety of organisms when fistula formation occurs or on repeated surgical interference.

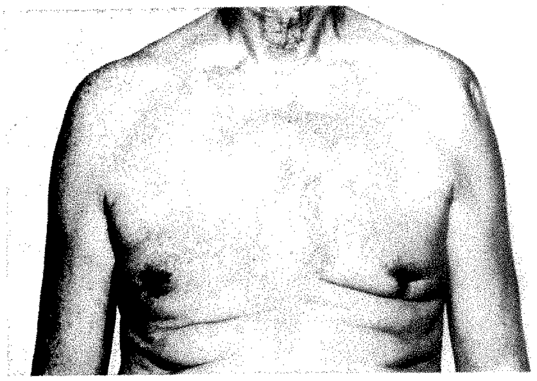

Fig. 3. *Case* 1. Showing the final postoperative appearance.

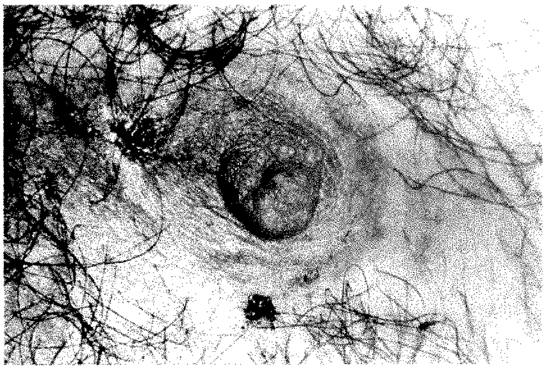

Fig. 4. *Case* 3. The left nipple, showing a sinus at 9 o'clock on the areolar margin.

The traditional view of the pathological events in duct ectasia as described by Haagensen (1971) is that dilatation of the terminal collecting ducts in the sub-areolar zone is the primary event, followed by distension with cellular debris and lipoid material. The duct epithelium atrophies and the lipoid material may extrude into the periductal tissues setting up a granulomatous inflammatory reaction. Finally, post-inflammatory fibrosis leads to ductal shortening and nipple retraction.

However, Dossett (1959) believes that the sequence of events is transposed and chronic periductal inflammation is the primary event. This results in destruction of the elastic network in the duct wall, leading to ductal dilatation. Histology of the excised breast tissue from the male patients presented here shows similar features to those described in the female by Dossett (1959). The predominant picture is that of focal granulomatous infiltration, which was well shown in *Case* 1. Tedeschi and McCarthy (1974) have reported a male with a histological diagnosis of periductal mastitis similar to that in the female, but the clinical presentation was that of a tender juxta-areolar lump. The periductal inflammation, when severe, shows as a density on mammography which is indistinguishable from gynaecomastia, as exemplified by our first case.

Treatment of these inflammatory lesions in the female by simple incision and drainage has been shown to predispose to recurrent fistula formation and this also appears to occur in the male, as shown in two of our case reports.

Curative treatment in the female depends on whether the abscess appears to be derived from single or multiple duct involvement; with the single duct entity treated by fistula excision, as described by Atkins (1955), and the multiple duct type by total duct excision, as described by Hadfield (Hughes, 1977).

The same principles apply presumably to male cases, although the role of the limited operation of fistula excision is uncertain at the present time; it was unsatisfactory in our *Case* 2. In the male, there are no cosmetic or functional considerations to contraindicate a formal duct excision, and this should probably be considered the treatment of choice in all cases.

Acknowledgements

Cases 1 and 2 underwent their definitive management under Professor L. E. Hughes. We are grateful to him for drawing our attention to the concept of duct ectasia in the male and to Mr M. Baum for allowing us to report *Case* 3.

References

ADAIR F. E. (1933) Plasma cell mastitis—a lesion simulating mammary carcinoma. *Arch. Surg.* **26**, 735–749.

ATKINS H. J. B. (1955) 'Mammary fistula'. *Br. Med. J.* **2**, 1473.

BONSER G. M., DOSSETT J. A. and JULL J. W. (1961) *Human and Experimental Breast Cancer*. London, Pitman Medical, pp. 237–265.

DOSSETT J. A. (1959) MD Thesis, University of London, p. 187.

HAAGENSEN C. D. (1971) *Diseases of the Breast*, 2nd ed. Philadelphia, Saunders, pp. 190–201.

HADFIELD G. J. (1960) Excision of the major duct system for benign disease of the breast. *Br. J. Surg.* **48**, 472–477.

HUGHES L. E. (1977) Operations for benign breast disease. In: ROB C. and SMITH R. *Operative Surgery: Breast and General Principles*, 3rd ed. London, Butterworths, pp. 64–78.

INGIER A. (1909) Ueber obliterierende Mastitis. *Virchows Arch.* **198**, 338–345.

TEDESCHI L. G. and MCCARTHY P. E. (1974) Involutional mammary duct ectasia and periductal mastitis in the male. *Hum. Pathol.* **5**, 232–236.

WALKER J. C. and SANDISON A. T. (1964) Mammary duct ectasia —a clinical study. *Br. J. Surg.* **51**, 350–355.

WOOD R. A. B., WILLIAMS R. H. P. and HUGHES L. E. (1977) Foam elastomer dressing in the management of open granulating wounds—experience with 250 patients. *Br. J. Surg.* **64**, 554–557.

Paper accepted 21 March 1979.

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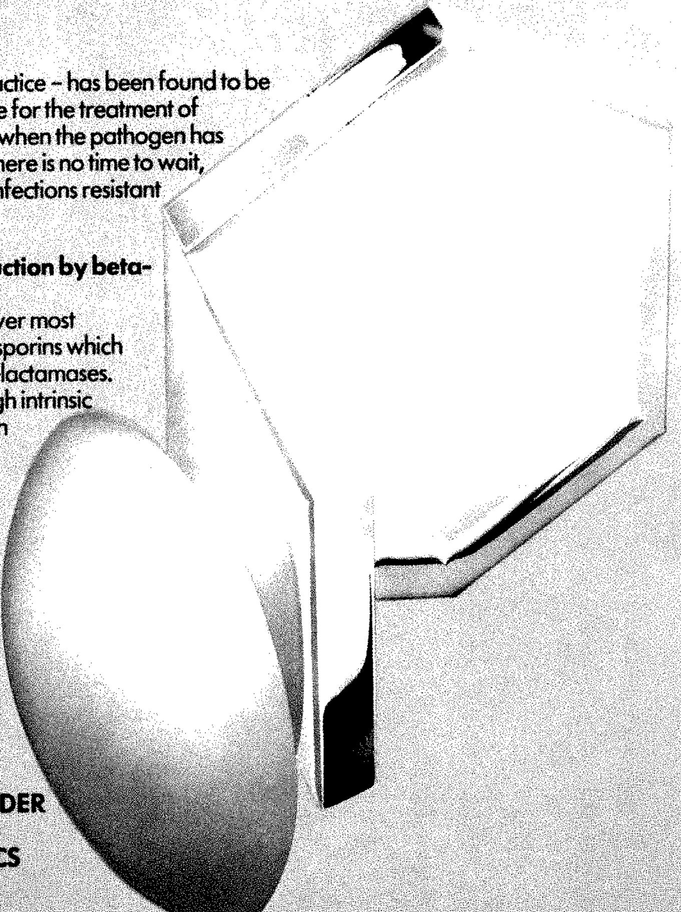

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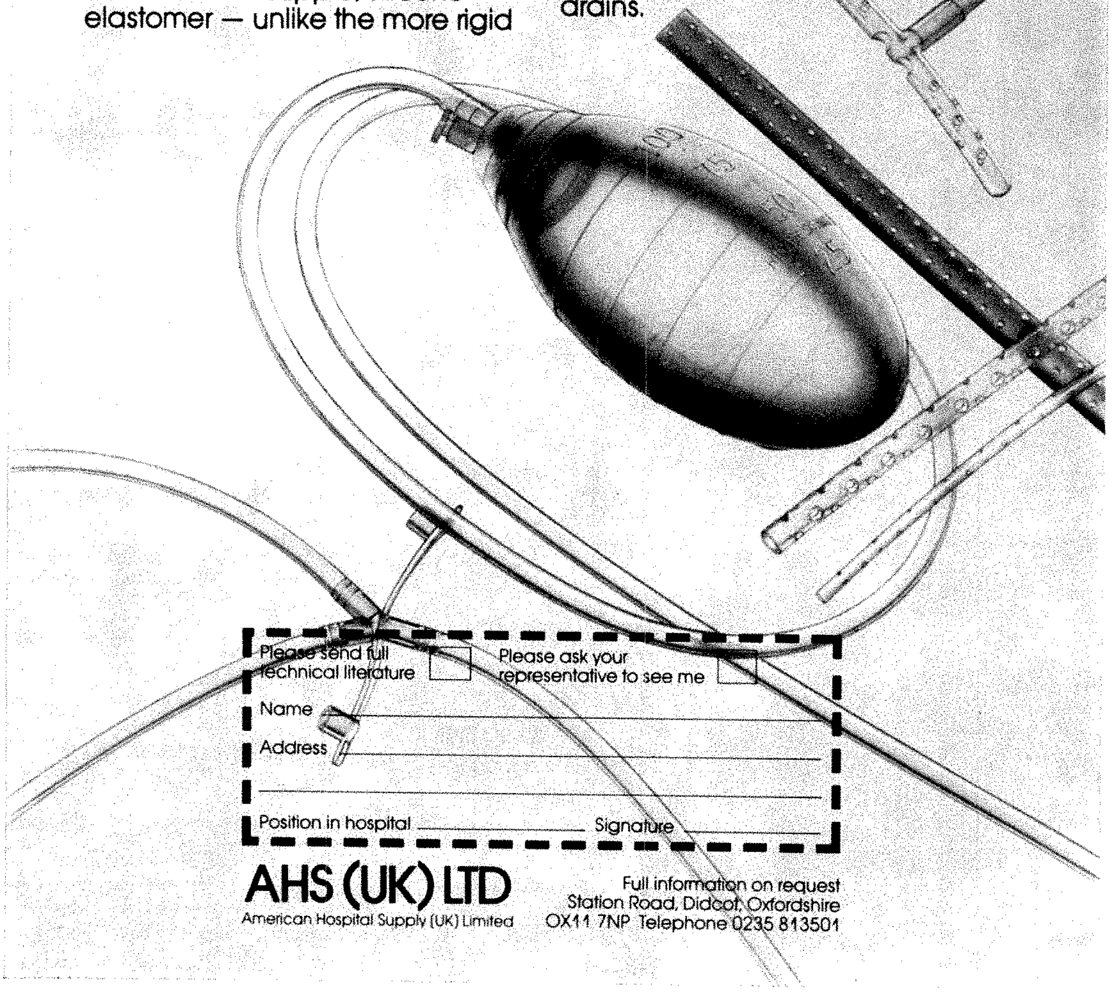

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Small bowel strictures after blunt abdominal trauma

C. G. MARKS, D. J. NOLAN, J. PIRIS AND C. U. WEBSTER*

SUMMARY

Two patients with strictures of the small intestine after blunt abdominal trauma are reported. In the first there were multiple severe injuries and the ileal stricture due to a mesenteric tear was not diagnosed until 6 weeks later. In the second an apparently minor injury was responsible for direct damage to the wall of the jejunum and a subsequent stricture.

Case reports

Case 1: D. W., a 30-year-old man, was admitted as an emergency on 12 February 1977 following a road traffic accident. His principal injuries were a rupture of the thoracic aorta, a Monteggia fracture of the right forearm and pelvic fractures.

The ruptured aorta was repaired on 14 February (Mr A. J. Gunning), when a virtually complete transection of the aorta, situated 3 cm beyond the origin of the subclavian artery, was replaced by a Dacron graft. Recovery was satisfactory.

Later during this admission it was noted that the patient's abdomen was distended for 5 days, a finding attributed to a paralytic ileus secondary to a retroperitoneal haematoma. He was discharged home on 15 March.

He was readmitted on 26 March (6 weeks after the accident) when he complained of severe, colicky, epigastric and central abdominal pain. He had not vomited and there was no history of bowel upset. On examination he was noted to be dehydrated and in severe pain. His abdomen was distended and there was marked epigastric tenderness.

Plain abdominal X-rays showed distended loops of small bowel and a diagnosis of subacute obstruction or an inflammatory mass was suggested. A small bowel barium infusion was therefore performed, which showed dilatation of the distal jejunum and proximal ileum. In the ileum there was complete hold-up of the contrast medium in front of the sacrum, where a small leak was demonstrated.

A laparotomy followed, when an ischaemic stricture of the ileum, with a sealed-off perforation, was found opposite a mesenteric tear and adherent to a pelvic fracture posteriorly. The stricture was resected and the postoperative course was uneventful. The patient was discharged on 5 April.

He was readmitted, however, on 13 April, when an intraperitoneal abscess was drained. No communication to the bowel was found and this wound was left open; it was noted to have healed completely on 30 June.

The histology of the resected bowel showed ischaemic necrosis of the whole thickness of the bowel wall.

Case 2: B. G., a 33-year-old man, was admitted as an emergency on 16 July 1978 with abdominal pain after being crushed for a few moments between a heavy motor roller and a wall. On examination he was not shocked; the only positive finding was tenderness across the epigastrium and left hypochondrium.

A plain abdominal X-ray showed no abnormality and a diagnosis of bruising of the anterior abdominal wall was made. He was observed for 24 h and sent home.

On 27 July he was seen again, at home, because he was feeling unwell, with loss of appetite. Eight days after his injury he had vomited, following a large meal, and subsequently had been unable to eat a full meal.

On examination he was tender across the lower third of the left rectus but there were no other abnormalities. He was given a bland diet. His symptoms improved but he still found that he was unable to eat a large meal without nausea and central abdominal pain. A barium meal was requested and showed a segment of narrowing in the proximal jejunum, which was confirmed by a small bowel barium infusion on 18 August.

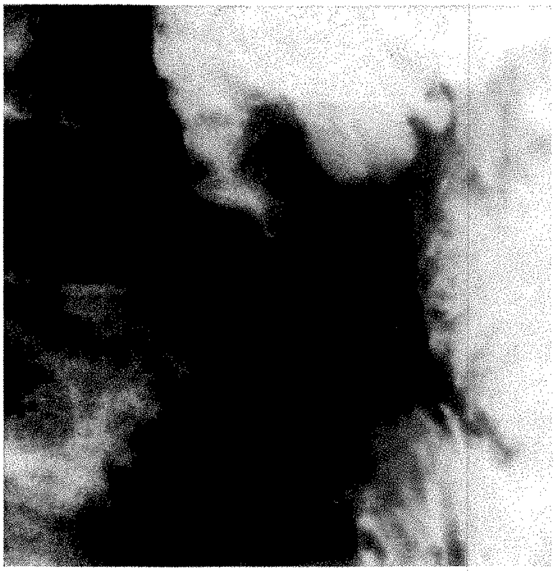

Fig. 1. A small bowel barium infusion showing a close-up of the jejunal stricture on an oblique spot view.

He continued to lose weight and a further small bowel infusion on 2 October (*Fig.* 1) showed that the bowel proximal to the stricture was more dilated. He was readmitted on 20 October.

A laparotomy was carried out, when a stricture in the jejunum, 1 m from the duodenojejunal flexure, was found wrapped in omentum. There was no evidence of perforation or a mesenteric tear. The stricture was resected and the patient made a satisfactory recovery, returning home on 29 October.

The histology of the stricture showed ischaemic damage to the outer coat affecting mainly the circular muscle with sparing of the submucosa and mucosa. However, these layers were infolded secondary to the fibrosis and contraction of the underlying muscle and thereby contributed to the obstruction.

Discussion

Strictures of the small intestine due to blunt trauma appear to be very rare (Marston, 1977). There was only one such stricture in a series of 95 benign strictures reported from Stockholm over a 12-year period up to 1968 (Räf, 1969). In 1967 Gillet et al. reported a stricture in a child aged 6 similar to that in our second patient. In a review of the literature these authors found 48 reports of post-traumatic stricture described since 1901. Two types of stricture were recognized, one due to direct trauma to the bowel wall and the other secondary to a mesenteric tear. The strictures were confined to the proximal and distal extremes of the small bowel where the bowel was relatively fixed—the proximal jejunum and terminal ileum. The mechanism of injury was thought to be shearing or tearing of the mesentery at the points

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of fixation. In addition, it has been suggested that these segments of small bowel are particularly liable to be crushed against the spine. Both the strictures presented here were close to the midline and in front of the spine.

A subserosal haematoma associated with the use of the lap-type seat belts (Tolins, 1964; Di Fiore and Gin, 1968) is one example of delayed presentation but there may be a long interval of up to several months or even years between the injury and the onset of symptoms. The symptoms may be acute, with complete obstruction or even perforation, as illustrated by our first patient, or chronic with abdominal pain and distension due to incomplete obstruction, as in our second patient. Where the possibility of a traumatic stricture is considered a small bowel barium infusion (Sellink, 1976; Nolan and Pantelidis, 1978) will usually demonstrate the stricture. This investigation helped in the management of both our patients and led to the correct preoperative diagnosis.

Acknowledgements

We are grateful to Mr N. E. Dudley for permission to report the first case.

References

DI FIORE F. R. and GIN OCK-MIN (1968) Injuries due to automobile seat belts. *Am. Surg.* **34**, 828–830.

GILLET M., PHILIPPE E. and ADLOFF M. (1967) Les sténoses cicatricielles de l'intestin grêle après contusion de l'abdomen. *J. Chir.* **93**, 469–477.

MARSTON A. (1977) *Intestinal Ischaemia.* London, Arnold.

NOLAN D. J. and PANTELIDIS N. (1978) Antegrade intubation barium examination of the small intestine. *Br. J. Radiol.* **51**, 154–158.

RÄF L. E. (1969) Ischaemic stenosis of the small intestine. *Acta Chir. Scand.* **135**, 253–259.

SELLINK J. L. (1976) *Radiological Atlas of Common Diseases of the Small Bowel.* Leiden, Stenfert Kroese.

TOLINS S. H. (1964) An unusual injury due to a seat belt. *J. Trauma* **4**, 397–399.

Paper accepted 3 April 1979.

Statistics in *The British Journal of Surgery*

It is part of the clinical scientist's stock-in-trade to use statistical methods. In many instances, and by most readers, these can be taken on trust, but in that there is a wide variety of tests and, on occasion, disagreement amongst both amateurs and professionals on the best choice, it is always wise that authors quote the method used. It is indeed journal policy to quote methods, the reason for their choice and, in the case of clinical trials, the confidence or tolerance limits of the observed results. Delay in acceptance may occur if contributors do not include these details.

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Total small bowel strangulation: a case report

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SUMMARY

A case of strangulation of the entire small intestine caused by an internal incarcerated hernia is presented. At laparotomy the small intestine was severely discoloured, paralytic and the viability of the bowel was questionable. No resection was performed. At a second laparotomy 10 h later the intestine was hyperaemic and exhibited lively motor activity. Recovery was complete. The importance of prolonged conservative management in avoiding extensive resection is stressed.

MASSIVE small bowel resection produces profound metabolic deficits but adequate nutrition is maintained unless the resection exceeds 50 per cent of the small bowel length (Koeberle, 1881; Haymond, 1935; Bothe et al., 1954) or a major portion of the ileum is resected (Booth, 1961). Preservation of the distal ileum and the ileocaecal valve prolongs the intestinal transit time and improves the absorption (Kalser et al., 1958). Early laparotomy is of great importance in patients suffering from mesenteric vascular occlusion or strangulating obstruction but at laparotomy it is sometimes difficult to determine the viability of the bowel and to define the limits of the segment to be resected.

Case report

A 36-year-old woman, who had previously undergone cholecystectomy and appendicectomy, was admitted to Sahlgrenska Sjukhuset, Göteborg, with a history of severe abdominal pain, starting in the right lower part of the abdomen 11 h earlier. She had been vomiting repeatedly and had had continuous pain. On admission the abdomen was distended and diffusely tender but there was no rigidity. A plain X-ray of the abdomen was normal. On examination 3 h later the patient was in great pain, pale and feverish. Her pulse was weak and rapid and her blood pressure was not measurable. The abdomen was distended and there was generalized tenderness with guarding.

At laparotomy, 16 h after onset of symptoms, the peritoneal cavity contained 500 ml of foul-smelling, turbid fluid. The small bowel was dilated and severely discoloured. The entire small bowel, with the exception of 15 cm proximally and 10 cm distally, was found to be rotated and strangulated by a loop of small bowel incarcerated through a hole in the mesentery at the ileocaecal angle (*Fig.* 1). The small bowel mesentery had a short base and the caecum was mobile, making rotation possible. The incarcerated loop was reduced and the intestine freed. As soon as the herniated loop was reduced and the mesentery untwisted a pulse could be felt in the mesentery. The bowel was totally paralytic, however, and did not react to mechanical stimulation. After 2 h the bowel was still blackish but some parts did react weakly to mechanical stimulation. The viability of the entire affected bowel was doubtful. Any excision would have been extensive and we therefore decided not to resect but to perform a second laparotomy later.

The first few postoperative hours were dramatic. The patient's circulation was very unstable, and in spite of intensive fluid replacement (about 1000 ml/h) she tended to go into hypovolaemic shock. The second laparotomy was carried out after 10 h. The peritoneal cavity now contained 2000 ml of odourless serosanguineous fluid. The bowel was purple–red, hyperaemic and exhibited very lively spontaneous motor activity (*Fig.* 2).

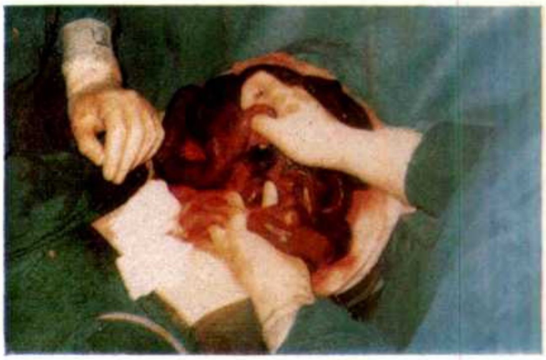

Fig. 1. The small bowel after the reduction of the strangulation. The assistant is holding two fingers through the hole in the mesentery.

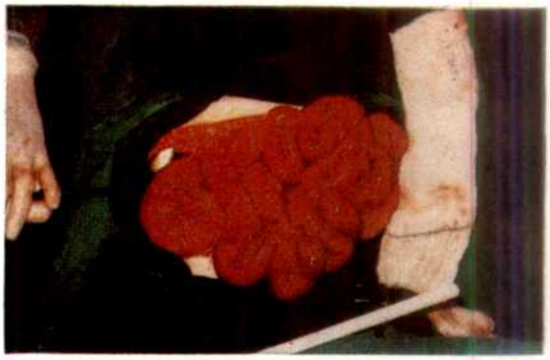

Fig. 2. The hyperaemic small bowel at the second laparotomy.

After the second laparotomy the patient's condition improved steadily. Altogether the patient was given 14 l of fluid during the first 24 h, including 2 units of blood, 1000 ml of Dextran 40, 500 ml of Dextran 70 and 4500 ml of plasma. The external losses measured during the same period were 7·8 l. The volumes of the losses and the fluid therapy decreased to normal values after 5 days. Oral fluid was started on the eighth day and parenteral nutrition was stopped on the eleventh day. Peritoneal lavage (totalling 13 l) was given during the first 3 days. Antibiotics (gentamicin and benzylpenicillin) were started at the primary operation and continued for 8 days. One dose of steroid (methylprednisolone 2 g i.v.) was given during the first operation.

Bowel motions started on the fifth day, with loose bloody stools containing tissue debris that may have been necrotic mucosa. The blood ceased after a week. During the period of hospital stay the number of stools decreased from 6–8 per day to 3–5 per day. The patient complained of postprandial abdominal pain.

A barium meal was performed on the eighth postoperative day. The passage was slow and barium reached the caecum in 16 h. The proximal part of the small bowel was slightly dilated with a normal mucosal relief pattern. The middle and distal parts showed severe changes, with a narrow, rigid lumen lacking the normal mucosal pattern. The changes resembled extensive, advanced Crohn's disease. A second barium meal on the eighteenth day showed a radiological improvement. A third barium meal after 3 months was normal.

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The patient was discharged from the hospital after 3 weeks. Within 2 months the stools were normal, with 1–2 motions a day, and the patient had regained her preoperative weight. After 4 months she was readmitted and operated upon for obstruction due to an adhesion. At this laparotomy the small bowel looked normal.

Discussion

Internal herniation is an uncommon cause of bowel obstruction. In this case it was combined with rotation of the whole small intestine and the caecum with strangulation of almost the entire small intestine. At operation there was peritonitis and most of the small bowel gave the impression of gangrene but there were still signs of viability, with pulsations in the mesentery and a weak reaction to mechanical stimulation in some parts of the affected bowel.

Any sign of viability was sufficient reason for not resecting since the unaffected small bowel was very short. Second laparotomy has previously been recommended after reconstructive vascular surgery on the superior mesenteric artery (Shaw and Magnard, 1958; Glotzer and Glotzer, 1966). After total occlusion of the superior mesenteric artery in dogs perforation may occur after 9–10 h (Marston, 1977). Less than 10 h between the first and the second laparotomy probably would have been long enough for exclusion of an irreversible infarction.

The consequences of intestinal strangulation are blood and plasma trapping, release of vasoactive substances and bacterial invasion of the wall of the gut. As long ago as 1934, Holt demonstrated the protective effect of saline transfusion following strangulation of the bowel. From animal experiments it is well known that revascularization of an ischaemic bowel is clearly unsafe, with increasing mortality, depending upon the duration of ischaemia (cf. Marston, 1977). Again, the protective effect of fluid therapy has been demonstrated (Marston, 1963; Chiu et al., 1972). The present case clearly illustrates the central role of fluid therapy in this condition. To maintain the balance we had to give about twice the measured volume of external losses. Milliken et al. (1965) reduced the mortality from revascularization in animal experiments by reducing endotoxin production. The antibiotics, the peritioneal lavage and the steroids might have contributed to our success. The benefit of low molecular weight dextran and other plasma substitutes in the treatment of intestinal shock has been studied by Dawidson et al. (1978).

References

BOOTH C. (1961) The metabolic effects of intestinal resection in man. *Postgrad. Med. J.* **37**, 725–739.

BOTHE F. A., MAGEE W. S. and DRISCOLL R. H. (1954) Massive resection of small intestine from 15 centimeters distal to ligament of Treitz to within 6 centimeters of ileocaecal valve, with 4 years' follow-up. *Ann. Surg.* **140**, 755–758.

CHIU C. S., SCOTT H. J. and GURD F. N. (1972) Volume deficit versus toxic absorption—a study of canine shock after mesenteric arterial occlusion. *Ann. Surg.* **175**, 479–488.

DAWIDSON I., HAGLIND E. and GELIN L.-E. (1979) Haemodilution and oxygen transport to tissue in shock. *Acta Chir. Scand.* (In the press.)

GLOTZER D. J. and GLOTZER P. (1966) Superior mesenteric embolectomy. Report of two successful cases using the Fogarty catheter. *Arch. Surg.* **93**, 421–424.

HAYMOND H. E. (1935) Massive resection of the small intestine. An analysis of 257 collected cases. *Surg. Gynecol. Obstet.* **61**, 693–705.

HOLT R. L. (1934) The pathology of acute strangulation of the intestine. *Br. J. Surg.* **21**, 582–587.

KALSER M. H., ROTH J. L. A. and TUMEN H. (1958) Relation of small bowel resection to nutrition in man. In: *Proceedings of a World Congress on Gastroenterology.* Baltimore, Williams & Wilkins, vol. 1, pp. 458–468.

KOEBERLE E. (1881) Resection de deux mètres d'intestin grêle suivie de guérison. *Gaz. Hebd. Méd.* **18**, 55–58.

MARSTON A. (1963) Causes of death in mesenteric arterial occlusion. *Ann. Surg.* **158**, 952–960.

MARSTON A. (1977) Laboratory studies of intestinal ischaemia. In: *Intestinal Ischaemia.* London,

MILLIKEN J., NAHOR A. and FINE J. (1965) A study of the factors involved in the development of peripheral vascular collapse following release of the occluded superior mesenteric artery. *Br. J. Surg.* **52**, 699–703.

SHAW R. S. and MAGNARD E. P. (1958) Acute and chronic thrombosis of the mesenteric arteries associated with malabsorption: a report of two cases successfully treated by thrombendarterectomy. *N. Engl. J. Med.* **258**, 874–878.

Paper accepted 2 April 1979.

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Randomized prospective matched pair study comparing peritoneovenous shunt and conventional therapy in massive ascites

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SUMMARY

A prospective randomized matched pair study was designed to test the efficacy of the peritoneovenous (LeVeen) shunt as a treatment for massive cirrhotic ascites compared with traditional medical therapy. Patients who failed to lose weight while on a low salt diet and fluids restricted to 1000 ml daily were placed in the study group. Weight loss, decrease in abdominal girth and diuresis were significantly greater ($P<0\cdot01$) for surgical patients than for their medically treated counterparts. The surgical technique is simple, quick and inexpensive. The surgical patients outlived their matched partners in 12 of 14 pairs where a definitive comparison was possible ($P<0\cdot02$). The median stay in hospital after randomization was shortened from 32 days with medical therapy to 15 days for those undergoing the shunt operation. Those treated medically experienced a significant rise in mean blood urea nitrogen and K^+ ($P<0\cdot02$). Patients with alcoholic hepatitis, hyperbilirubinaemia (bilirubin >154 μmol/l), peritoneal sepsis, severe coagulopathy and those who had recently bled from oesophageal varices are poor risks for the surgical procedure.

THE onset of ascites in cirrhosis is a critical turning point in the course of hepatic decompensation. Medical management is based on salt and water restriction and diuretic therapy. Overutilization of diuretics may deplete the intravascular fluid compartment and precipitate functional renal failure. Oliguria, azotaemia or stubborn resistance to drug therapy herald a poor prognosis (Garceau and Chalmers, 1963; Conn, 1973). Insertion of the LeVeen peritoneovenous shunt in such patients has been shown to overcome refractory ascites and even reverse the hepatorenal syndrome (LeVeen et al., 1976; Reinhardt and Stanley, 1977; Wapnick et al., 1977, 1978; Grosberg and Wapnick, 1978).

A randomized prospective matched pair study was designed to compare the LeVeen shunt with conventional therapy in patients with cirrhotic ascites. The present manuscript describes the results of this trial conducted over a 2-year period.

Patients and methods

Between July 1975 and June 1977, cirrhotic patients admitted to the Gastrointestinal Medical Service of the Brooklyn Veterans Administration Hospital with ascites were placed initially on a diet containing 500 mg of sodium with water limited to 1000 ml per day. The age, duration of illness and associated medical diseases were recorded. Daily weights, measurement of abdominal girth and twice-weekly estimation of blood urea nitrogen, serum creatinine, electrolytes, bilirubin, liver function tests, urine flow, urine creatinine and Na^+ were determined. Progress was reviewed after 14 days. If the ascites and body weight had not decreased, and oliguria persisted, the patient was randomly entered into the prospective study unless the patient refused or a specific complication precluded one or other of the treatment protocols.

Patients with known peritoneal or systemic infection, congestive heart failure, primary renal disease or recent evidence of variceal bleeding were excluded. Cirrhotics in stage III or IV hepatic encephalopathy or jaundice (bilirubin >154 μmol/l) were also excluded. However, if liver function or mental status improved, such patients were entered into the study if massive ascites persisted or the hepatorenal syndrome supervened.

Patients were stratified into three groups according to the highest serum bilirubin level on the current admission (*Table I*). The patients were further divided into a high creatinine (>177 μmol/l) and low creatinine group. Randomization to either medical or surgical therapy for patients was then achieved on the same day by pulling a number from an envelope. Patients in the medical group were matched with those in the surgical group according to the subgroups listed in *Table I* and sequentially according to the date of entry into the study. This study was approved by the Human Studies Committee of the Brooklyn Veterans Administration Hospital. Each patient agreed to both forms of therapy before entering the study. Thirty-four patients were entered into the study and all completed the randomly assigned therapy.

Medical therapy

The sequential dose and type of diuretic therapy are shown in *Table II*. Diuretic therapy was withheld if azotaemia (BUN > 5 mmol/l) was present. Frusemide (furosemide) was administered if hyperkalaemia (serum K>5 mmol/l) was present or if the patient had become refractory to the diuretics listed in *Table II*.

Table I: STRATIFICATION IN RANDOMIZED STUDY

Group	Admission bilirubin (μmol/l)*	No. of pairs	No. of pairs Cr>177 μmol/l
I	<34	4	1
II	34–83	5	1
III	83–154	8	3

* Highest bilirubin during 2 weeks prior to randomization.

Table II: METHOD OF DIURETIC ADMINISTRATION

a. If low salt diet is unsuccessful, then:
    Aldactone 200 mg/day × 4 days
b. If 200 fails, then:
    Aldactone 400 mg/day × 4 days
c. If 400 fails, then:
    Aldactone 600 mg/day × 4 days
d. If 600 fails, then:
    add chlordiazide 50 mg/b.i.d.
    or
    frusemide 40–80 mg/t.i.d.

Surgical therapy

The preoperative preparation, operative technique and postoperative care have been described elsewhere (LeVeen et al., 1976; Wapnick et al., 1977). The operation performed under

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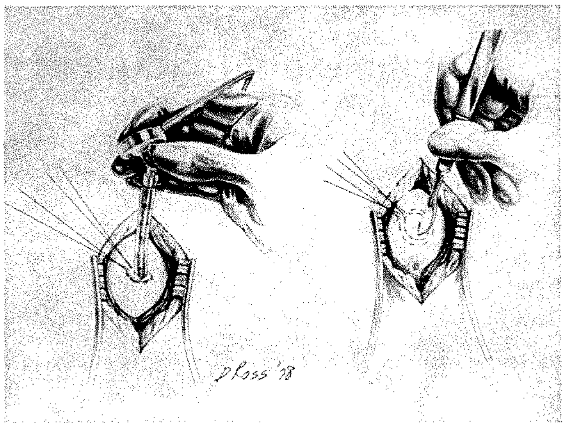

Fig. 1. LeVeen peritoneovenous shunt. A wide perforated portion is inserted into the peritoneal cavity: the valve is placed extraperitoneally and Silastic tubing tunnelled subcutaneously to the neck where it is inserted into the superior vena cava.

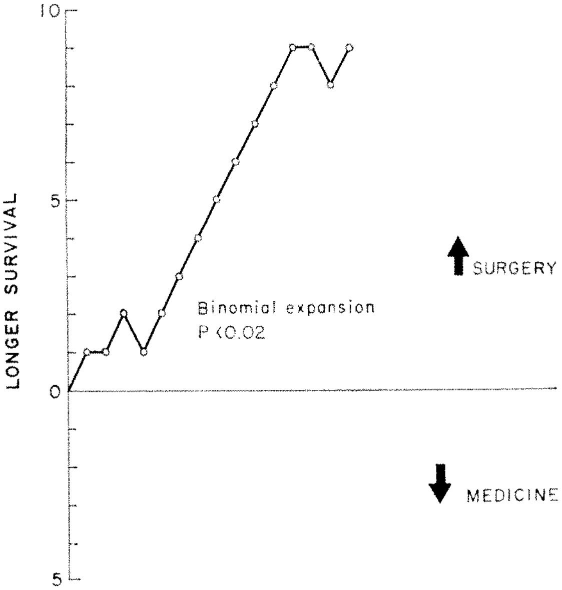

Fig. 2. Matched pair analysis of survival. Patients undergoing the shunt operation showed significant prolongation in survival compared with those treated by conventional methods (binomial expansion: $P<0{\cdot}02$).

local anaesthesia is relatively minor. Ascitic fluid is drained through a wide perforated Silastic tube into a one-way valve that is located extraperitoneally. A long, narrow silicone rubber tube attached to the valve is tunnelled subcutaneously to reach the neck where it is inserted into the superior vena cava (*Fig.* 1). To facilitate drainage through the valve after operation, the patient remains supine, an abdominal binder is worn and exercises designed to encourage maximal inspiratory effort are performed. Frusemide, 40–80 mg every 4–8 h, is administered intravenously initially and tapered after 3–4 days according to individual requirements. Dietary sodium intake after operation was between 1 and 2 g. Diuretics were prescribed if ascitic fluid reaccumulated at any stage in the postoperative period. Implanted valves have functioned satisfactorily for 3–4 years after insertion (LeVeen et al., 1976; Wapnick et al., 1978).

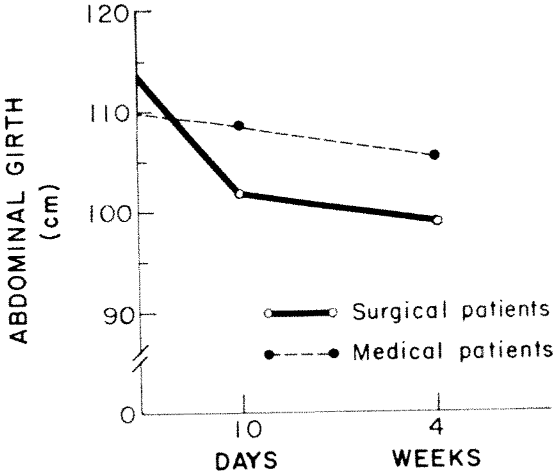

Fig. 3. Patients treated with peritoneovenous shunt showed significantly ($P<0{\cdot}001$) greater mean net loss in abdominal girth measurement.

Table III: SURVIVAL FOLLOWING RANDOMIZATION OF PATIENTS TREATED BY MEDICAL THERAPY OR THE PERITONEOVENOUS SHUNT OPERATION

Months after randomization	Medical treatment No.	Medical treatment % alive	PV shunt No.	PV shunt % alive
0	17	100	17	100
3	6	35	11	65
6	5	29	8	47
12*	1	6	7	41
24*	1	6	5	29
36			3†	

PV, Peritoneovenous.

* Differences between values are considered significant if they exceed twice the standard error of difference.

† Two patients still alive are excluded as follow-up after shunt is less than 3 years. One patient in medical group was lost to follow-up 28 months after randomization.

The following measurements were performed before randomization: body weight, abdominal girth (at the umbilical level), 24-hour urine volume, complete blood count, serum electrolytes, creatinine, BUN, total protein, albumin and urine sodium and creatinine. Measurements were repeated 10 days after randomization. In both groups, data were collected at 4 weeks and on subsequent outpatient visits. The length of hospital stay and the development of complications were recorded.

Differences between medical and surgical patients were tested by the Wilcoxon test. Changes over the course of therapy for both groups were evaluated by the Friedman two-way analysis of variance. Results for survival were scored as positive for either treatment group (binomial expansion) if the patient survived at least 3 weeks longer than his matched partner.

Results

Of the 17 matched pairs, 12 surgical patients outlived their corresponding medical partners. Two medical patients lived longer than their surgical counterparts using the same criteria. Two pairs survived the same length of time. In one pair both individuals are still alive. It was thus possible to assess the difference in survival in 16 pairs.

Surgical therapy offered significant prolongation of survival (binomial expansion, $P<0{\cdot}02$, *Fig.* 2). Two

Table IV: EXPERIMENTAL DATA OVER TIME FOR MEDICAL AND SURGICAL PATIENTS (mean±s.d.)

Parameter	Wilcoxon test*	Patient group	Friedman two-way anova†	Pre-therapy	10 d	4 wk
Weight (kg)	$T = 20$ $P < 0{\cdot}01$	Medical	$X/^2_r = 9{\cdot}5$ $P < 0{\cdot}01$	80·9±18·2 (17)	77·2±18·9 (16)	70·4±10·8 (11)
		Surgical	$X/^2_r = 15{\cdot}0$ $P < 0{\cdot}001$	85·0±20·0 (16)	73·7±13·0 (16)	71·2±15·8 (9)
Abdominal girth (cm)	$T = 8$ $P < 0{\cdot}01$	Medical	n.s.	109·7±14·9 (15)	108·6±16·8 (15)	105·2±23·8 (12)
		Surgical	$X/^2_r = 26{\cdot}0$ $P < 0{\cdot}001$	113·8±15·5 (17)	101·1±13·3 (17)	98·9±18·2 (10)
Creatinine (μmol/l)	n.s.	Medical	n.s.	123·8±61·88 (17)	150·3±123·8 (17)	203·3±185·6 (17)
		Surgical	n.s.	123·8±88·4 (17)	132·6± 88·4 (15)	114·9±44·2 (7)
Creatinine clearance (ml/min)	n.s.	Medical	n.s.	15·8±15·2 (10)	47·2±45·6 (12)	
		Surgical	n.s.	36·6±35·5 (14)	140·7±344·9 (15)	
BUN (mmol/l)	n.s.	Medical	$X/^2_r = 7{\cdot}9$ $P < 0{\cdot}02$	4·2±4·15 (17)	4·8±5·2 (16)	7·6±7·5 (12)
		Surgical	n.s.	3·4±2·8 (17)	3·1±2·4 (14)	5·1±3·4 (9)

* Differences between the therapeutic regimens.
† Differences among the time periods.
The numbers in parentheses represent the number of subjects. Differences are due to patients having either left the hospital or died.

Table V: EXPERIMENTAL DATA OVER TIME FOR MEDICAL AND SURGICAL PATIENTS (mean±s.d.)

Parameter	Wilcoxon test*	Patient group	Friedman two-way anova†	Pre-therapy	10 d	4 wk
Na^+ (mmol/l)	n.s.	Medical	n.s.	131·3±7·6 (16)	130·5±6·0 (15)	130·8±6·6 (12)
		Surgical	n.s.	131·9±5·2 (17)	133·9±5·2 (14)	134·7±5·4 (9)
Ca^{2+} (mmol/l)	n.s.	Medical	n.s.	2·2±0·25 (17)	2·2±0·25 (17)	2·2±0·25 (11)
		Surgical	n.s.	2·1±0·13 (17)	2·13±0·25 (15)	2·05±0·2 (7)
P^- (mmol/l)		Medical	n.s.	1·1±0·2 (14)	1·2±0·2 (13)	1·35±0·6 (11)
		Surgical	n.s.	1·1±0·3 (17)	1·1±0·5 (15)	1·0±0·2 (7)
K^+ (mmol/l)	$T = 15$ $P < 0{\cdot}02$	Medical	n.s.	4·5±0·5 (16)	5·0±0·5 (15)	5·1±0·9 (12)
		Surgical	n.s.	4·4±0·7 (17)	3·9±0·7 (14)	4·7±0·9 (9)

* Differences between the therapeutic regimens.
† Differences among the time periods.
The numbers in parentheses represent the number of subjects. Differences are due to patients having either left the hospital or died.

patients were shunted but at the time of completion of the study were not paired with a medically treated partner. Both patients responded favourably to the shunt and remained well and free of ascites at the conclusion of this study. Long term survival is shown in *Table III*. Median survival time for the pairs whose members have expired (9) was 57 days for those treated medically and 86 days for those shunted. The median hospital stay for pairs whose members left the hospital in good condition (9) was 32 days for those treated medically and 15 days for those shunted. Of the patients who were discharged, 5 in the medical group (median stay 26 days) and 7 of the surgical group (median stay 10 days), required readmission to the hospital.

The mean weight reduction was greater 10 days after treatment in the shunted patients (11·3 kg *v.* 3·7 kg) (*Table IV*). Both medical and surgical patients experienced significant weight reduction 4 weeks after randomization. A very significant reduction ($P < 0{\cdot}001$) in mean abdominal girth occurred in surgical patients over the first 10 days (12·7 cm) and at 4 weeks (14·9 cm) (*Table IV*). There was no significant change for medical patients at either time (1·1 cm and 4·2 cm respectively, *Table IV*). Maximal daily urine output was also significantly greater ($P < 0{\cdot}01$) in the surgical group during the first 10 days than in the medical group (medians 5815 ml *v.* 900 ml).

No significant changes occurred in the serum creatinine, albumin, sodium, calcium, phosphorus or creatinine clearance (*Tables IV* and *V*) during the treatment period in either the medical or the surgical patients. The medical patients, however, experienced a significant rise in BUN, whereas those shunted did not. Serum potassium was also elevated during medical therapy and lowered by operation (*Table V*).

The complications following medical and surgical therapy will be discussed elsewhere.

Discussion

In the United States alcohol abuse and its sequelae ranks as one of the five leading causes of death. Alcohol contributes significantly to absenteeism, decreased worker productivity and national morbidity statistics. The onset of ascites in the cirrhotic patient carries a grave prognosis (Garceau and Chalmers, 1963; Conn, 1973).

Conventional therapy of ascites aims at decreasing fluid accumulation by salt restriction and diuretics. Therapy for 'massive' ascites is usually ineffective.

Paracentesis and intermittent reinfusion of ascitic fluid rapidly decreases abdominal girth and results in weight reduction but has not significantly prolonged life (Clermont et al., 1967). Paracentesis, by precipitating a rapid fall in intravascular fluid volume, can be lethal (Papper, 1958). The continuous return of ascitic fluid to the venous system, when initiated at a time when the kidneys are refractory to diuretic therapy, is central to the success of the shunt (LeVeen et al., 1976; Wapnick et al., 1977). The surgical shunt corrects truly refractory ascites and the hepatorenal syndrome (Fuller, 1977; Wapnick et al., 1978). The present study shows that the insertion of the peritoneovenous shunt at an earlier stage offers significant prolongation of survival, more rapid correction of ascites and a shorter hospital stay. The therapy also protected against azotaemia, which was present 4 weeks after randomization in the non-surgical group.

The shunt operation should not be advocated indiscriminately for massive ascites (LeVeen et al., 1976; Wapnick et al., 1978). The incidence of postoperative complications and death is markedly increased in cirrhotics with jaundice (bilirubin greater than 153·9 μmol/l) or encephalopathy (Wapnick et al., 1978). Surgery should be considered if improvement in hepatic functions occurs but ascites persists or the hepatorenal syndrome supervenes. Removal of ascitic fluid prior to completion of the shunt procedure is indicated in the poor risk patient (Wapnick et al., 1978). There are several theoretical advantages to this approach. Fluid removal precludes the entry into the circulation of large amounts of ascitic fluid containing endotoxin (Tarao et al., 1977), thromboplastin-like materials (Lerner, 1971) and other as yet undetermined factors which may compromise the outcome. Tarao et al. (1977) in Japan noted that 17 of 23 (79·3 per cent) cirrhotic patients had endotoxin in the ascitic fluid. Recirculation of ascitic fluid by the peritoneovenous shunt did increase systemic endotoxin levels in 8 patients we have studied without any apparent adverse effects (unpublished data). Discarding of nearly all ascitic fluid at the time of surgery may also increase the safety margin of the shunt operation in preventing pulmonary oedema and cardiac failure as the intravascular compartment now receives ascitic fluid at a much slower rate. In the present study ascitic fluid was not discarded at the time of surgery. Further studies are indicated to predict preoperatively which components of ascitic fluid are likely to lead to complications. The possible role of haemodialysis combined with continuous fluid reinfusion requires further evaluation in patients in poor risk categories.

Patients with peritoneal sepsis (Conn, 1964) have a grave prognosis, and shunting of infected peritoneal fluid could lead to severe fulminating septicaemia. The shunt procedure is also contraindicated in patients with severe coagulation defects and those with recent variceal bleeding who have not had a decompressive procedure performed.

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References

CLERMONT R. J., VLAHCEVIC R.,
Intravenous therapy of ma
cirrhosis: II. Long term eff
of renal failure. *Gastroenter*
CONN H. O. (1964) Spontaneous
Laennec's cirrhosis cause
relatively common but rare
Intern. Med. **60**, 568–580.
CONN H. O. (1973) A rational
syndrome. *Gastroenterology*
FULLEN W. O. (1977) Hepator
peritoneovenous shunt. *Sur*
GARCEAU A. J. and CHALMERS T. C
cirrhosis. *N. Engl. J. Med.*
GROSBERG S. J. and WAPNICK S.
parison of functional renal
conventional therapy or
(LeVeen). *Am. J. Med. Sci.*
LERNER R. G. (1971) Stimulation
plastin activity by endotox
138, 145–148.
LEVEEN H. H., WAPNICK S. and
Further experience with
ascites. *Ann. Surg.* **184**, 574
PAPPER S. (1958) The role of the
of the liver. *Medicine* **37**, 29
REINHARDT G. F. and STANLEY
shunting for ascites. *Surg.*
TARAO K., SO K., MOROI T. et al.
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WAPNICK S., GROSBERG S. J., KI
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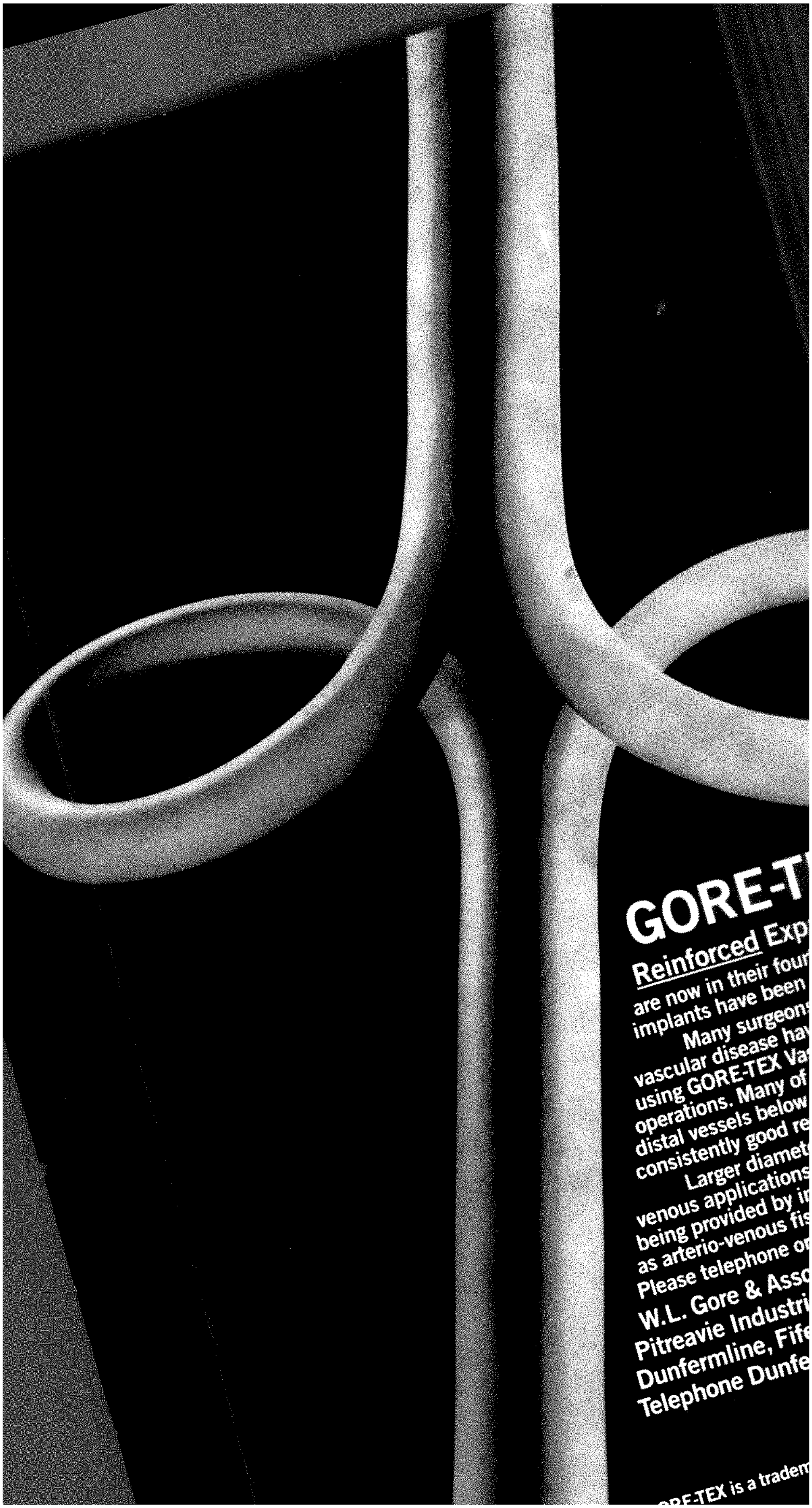

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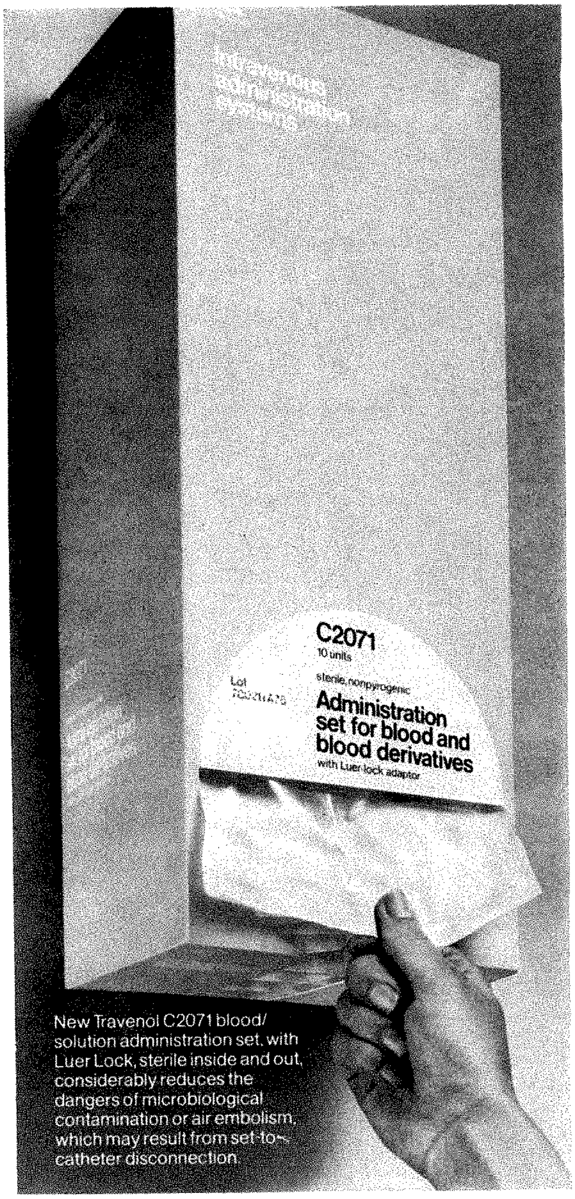
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Br. J. Surg. Vol. 66 (1979) 671–672

Preservation of the injured spleen*

MICHEL S. SLIM, NAJWA E. NAJJAR AND HENRY G. MISHALANY†

SUMMARY

Experience with suture repair of splenic lacerations in 14 children and 8 adults is reported. The youngest patient was 3 days old and the oldest 60 years. Adequate healing was confirmed by postoperative splenic scans with or without arteriography. The 2 deaths in this series were not related to the splenic repair and were due to associated major injuries. The course of illness in the remaining 20 survivors did not reveal a failure of this technique or a complication related to the use of this conservative approach. It is expected that salvage of the traumatized spleen will eliminate the risk of fulminant postoperative infections that may be fatal.

THE classic treatment recommended for a splenic injury is splenectomy. This may be followed by an overwhelming infection that can be fatal, especially in young children, and this can occur several years after operation (Ellis and Smith, 1966; Erickson and Burgert, 1968; Isa et al., 1974; Balfanz et al., 1978). This increased susceptibility to infection has been attributed to a decrease of IgM after splenectomy (Eraklis et al., 1967; Najjar et al., 1968; Walker, 1976) and to a disappearance of tuftsin, the phagocytosis-promoting peptide (Ellis and Smith, 1966; Najjar et al., 1968; Najjar and Nishika, 1970).

In view of the frequency of these serious postoperative septic complications, preservation of the traumatized spleen becomes imperative when this is technically possible. The present report is concerned with the conservative operative approach to splenic injuries in 22 patients admitted to the American University of Beirut Hospital during the period between 1 January 1973 and 31 December 1977.

Patients and methods

During the 5-year period studied 84 patients with splenic injuries were operated on, of whom 62 (73·8 per cent) required total extirpation of the spleen. Of the remainder, one patient underwent a partial splenectomy and 21 had suture repair of the splenic laceration. These cases form the subject of this report.

Fourteen patients were children, their ages ranging between 3 days and 15 years, and 8 were adults, the oldest being 60 years of age. In 12 patients the splenic injury was due to blunt trauma, in 9 patients it was inflicted by bullets or shrapnels and in 1 case, a 3-day-old infant, the cause of the laceration could not be ascertained.

Nineteen patients (86 per cent) had associated injuries to other organs or structures. In the case of blunt trauma, head injuries predominated, but other injuries to the chest, kidneys and extremities were also encountered. In the case of penetrating injuries, the associated lesions involved mainly the intra-abdominal organs and, less frequently, the lungs, head, peripheral vessels and bones.

The type of splenic injury varied from a single superficial laceration in 10 patients, to multiple lacerations of different depths in 7 patients and to deep lacerations with almost complete separation of the splenic segments in 5 patients. The surgical repair of splenic lacerations was accomplished by sutures of chromic catgut threaded on liver needles. An omental patch was included in the suture line in 5 cases and Gelfoam was applied over the site of repair in another 2 cases. The average duration of the procedure was 2 h when the injury was isolated to the spleen. Drains were left intraperitoneally at the end of operation in 6 of the 22 patients. Drains were used when the injury involved the gastrointestinal tract or liver or when there was associated retroperitoneal bleeding. Drains were also used in the case of partial splenectomy. The drains were removed either 48 h or 7 days after operation. Broad spectrum antibiotics were administered systemically in the majority of patients. The period of hospitalization ranged from 6 to 15 days with an average of 11 days for children and 23 days for adults, the longer period being observed in patients with multiple injuries.

Results

Two deaths occurred, both in the adult age group. One patient, who was 22 years old, had injuries involving the spleen, lungs, bowel and iliac vessels. He developed peritonitis, renal failure and bleeding from the iliac region which led to his death 5 days after operation. The other patient, who was 31 years old, had injuries involving the spleen, liver, lung, gastrointestinal tract and extremities. He succumbed on the eighth postoperative day. In the remaining 20 survivors, complications were noted in 4 patients. They consisted of wound haematoma and atelectasis with pneumonia in 2 children and superficial wound infection due to *Escherichia coli* in 2 adults.

A clinical follow-up ranging from 1 month to 2 years was obtained on 11 of the 20 survivors. The remainder could not be traced and the course of their illness after discharge remains unknown.

In 9 patients adequacy of the healing was checked by a splenic scan, using technetium sulphur colloid. The scan was done from 9 days to 2 years after operation. On 7 scans healing was reported to be normal. On 2 the scar in the spleen was visible radiologically as a linear defect. In one child whose spleen was fractured into two pieces a splenic arteriogram and scan were performed on the ninth day and repeated 2 months after operation, confirming complete healing of the laceration. In cases where splenic scans were done sequentially to determine the progress of healing, the uptake of the isotope, which was decreased initially, became normal in later studies.

Discussion

Until recently, splenectomy has been recommended as the best treatment for splenic lacerations. Our recent experience suggests that this is necessary in less than one-half of the cases; the remainder can be managed successfully by a primary repair of the laceration *in situ*. The safety of the latter technique is confirmed by the long term observation of these patients. Preservation of the spleen deserves serious consideration in all age groups especially children, in order to avoid the development of overwhelming infections secondary to asplenia (Editorial, 1976; Ravry et al., 1972).

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The conservative surgical approach to splenic injuries dates back to 1945 (Foster and Prey, 1940; Mazel, 1945). Work on preservation of the traumatized spleen in the experimental animal dates back to 1962 (Christo, 1962; Morgenstern et al., 1966; Morgenstern, 1974; Fitzer, 1976). No successful results were achieved until Bodon and Verzosa (1967) reported the use of Gelfoam for iatrogenic splenic injuries. Douglas and Simpson (1971) reported their experience with the conservative non-operative management of splenic trauma and contested that bleeding from a splenic laceration had usually stopped by the time of laparotomy. Microcrystalline collagen haemostat (Avitene) was reported useful in the control of bleeding from the spleen (Hait, 1970; Morgenstern, 1974). The application of peritoneal patches and butyl-2-cyanoacrylate monomer was also found by Orda et al. (1974) to be beneficial for the repair of splenic lacerations. Encouraged by these results, one of us reported his experience on surgical repair of the injured spleen in 8 children (Mishalany, 1974).

Acknowledgements

The authors gratefully acknowledge the support of the staff of the Departments of Radiology and Surgery in the collection, surgical management and evaluation of the cases included in this review.

References

BALFANZ J. R., NESBIT J. R., JARVIC C. et al. (1976) Overwhelming sepsis following splenectomy for trauma. *J. Pediatr.* **88**, 458–460.

BODON G. R. and VERZOSA E. S. (1967) Incidental splenic injury: is splenectomy always necessary? *Am. J. Surg.* **113**, 303–304.

CHRISTO M. C. (1962) Segmental resection of the spleen. *Hospital* (*Rio*) **62**, 575–590.

DOUGLAS G. J. and SIMPSON J. S. (1971) The conservative management of splenic trauma. *J. Pediatr. Surg.* **6**, 565–569.

EDITORIAL (1976) Infective hazards of splenectomy. *Lancet* **1**, 1167–1168.

ELLIS E. F. and SMITH R. T. (1966) The role of the spleen in immunity. *Pediatrics* **37**, 111–119.

ERAKLIS A. J., KEVY S. V., DIAMOND L. K. et al. (1967) Hazard of overwhelming infection after splenectomy in childhood. *N. Engl. J. Med.* **276**, 1225–1229.

ERICKSON W. D., BURGERT E. O. and LYNN H. B. (1968) The hazard of infection following splenectomy in children. *Am. J. Dis. Child.* **116**, 1–12.

EYKYN S. J., THOMAS R. D. and PHILLIPS I. (1974) Haemophilus influenza meningitis in adults. *Br. Med. J.* **2**, 463–465.

FITZER P. M. (1976) Scanning in the diagnosis of hepatic and splenic trauma. *Virg. Med. Monthly* **103**, 30–33.

FOSTER J. M. and PREY D. (1940) Rupture of the spleen. *Am. J. Surg.* **47**, 487–501.

HAIT M. R. (1970) Microcrystalline collagen: a new hemostatic agent. *Am. J. Surg.* **120**, 330.

ISA S. S., MIRHIJ N. J., FIRZLI S. S. et al. (1974) Post-splenectomy infections in childhood. *Z. Kinderchir.* **14**, 245–251.

MAZEL M. S. (1945) Traumatic rupture of the spleen. *J. Pediatr.* **26**, 82–88.

MISHALANY H. (1974) Repair of the ruptured spleen. *J. Pediatr. Surg.* **9**, 175–178.

MORGENSTERN L. (1974) Microcrystalline collagen used in experimental splenic injury: a new surface hemostatic agent. *Arch. Surg.* **109**, 44–47.

MORGENSTERN L., DICKMAN J. and SHORE M. (1966) Splenic hemostasis. In: *Proceedings of the Symposium of Physiologic Adhesives.* Houston, University of Texas, Graduate School, Biochemistry Society.

NAJJAR V. A., FIDALGS B. V. and STILL E. (1968) The physiological role of the lymphoid system VII. The disappearance of leukokinin activity following splenectomy. *Biochemistry* **7**, 2376–2379.

NAJJAR V. A. and NISHIOKA K. (1970) Tuftsin: a natural phagocytosis-stimulating peptide. *Nature* (*Lond.*) **228**, 672–673.

ORDA R., WIZNITZER T., GOLDBERG G. M. et al. (1974) Repair of hepatic and splenic injuries by autoplastic peritoneal patches and butyl-2-cyanoacrylate monomer: an experimental study. *J. Surg. Res.* **17**, 365–374.

RAVRY M., MALDONADO N., VELEZ-GARCIA E. et al. (1972) Serious infections after splenectomy in Hodgkin's disease. *Ann. Intern. Med.* **77**, 11–14.

WALKER W. (1976) Splenectomy in childhood: a review in England and Wales, 1960–1964. *Br. J. Surg.* **63**, 36–43.

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Br. J. Surg. Vol. 66 (1979) 673–674

The use of the Hickman catheter in the management of patients with leukaemia and other malignancies

MEIRION THOMAS

SUMMARY

The use of the Hickman right atrial catheter in 25 patients with leukaemia and other malignancies is reported, and it is concluded that with careful selection of patients, the benefits of this semi-permanent catheter outweigh the risks of infection. The catheter may be useful in the intensive care of children or adults with non-malignant conditions.

PROLONGED failure of bone-marrow and the gastrointestinal tract are frequent complications of cancer treatment by methods such as high-dose chemotherapy or total body irradiation with allograft bone-marrow reconstitution. Efficient long term access to the central circulation for haematological, antibiotic and nutritional support is essential in the management of such patients.

Patients and methods

The Hickman right atrial catheter (*Fig.* 1) consists of a 90-cm length of Silastic tubing with a connector at one end which can either be attached to an intravenous infusion set or sealed with a catheter cap after anticoagulating the catheter with 2 ml of 500 units/ml heparin. A Dacron cuff is glued a third of the way along the catheter and this becomes invaded by healing tissues to provide fixation and to protect against infection tracking along the outside of the catheter.

The catheter is most conveniently inserted into the cephalic vein at the deltopectoral groove under local or general anaesthesia (*Fig.* 2). After ensuring that the isolated cephalic vein is patent and wide enough to take the catheter a long subcutaneous tunnel is constructed with a straight artery forceps to come out low on the anterior chest wall. The catheter tip is grasped in the jaws of the artery forceps and the catheter is drawn through the subcutaneous tunnel until the Dacron cuff lies midway between the exit site and the vein. The length of Silastic tubing required to reach the midpoint of the right atrium is estimated and the catheter trimmed appropriately before threading into the cephalic vein. The position of the catheter must be checked by X-ray or fluoroscopy, and revised

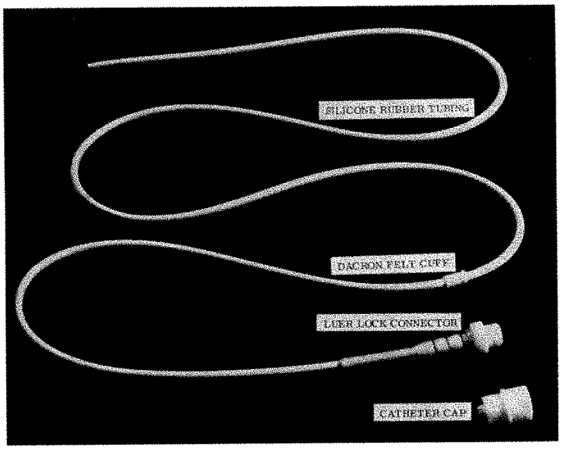

Fig. 1. The Hickman right atrial catheter.

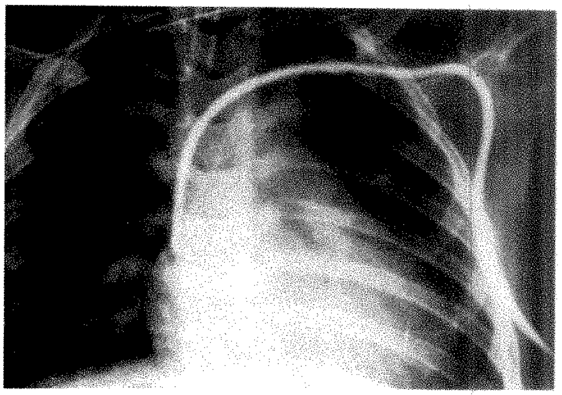

Fig. 2. The Hickman catheter inserted through the left cephalic vein in a 5-year-old child.

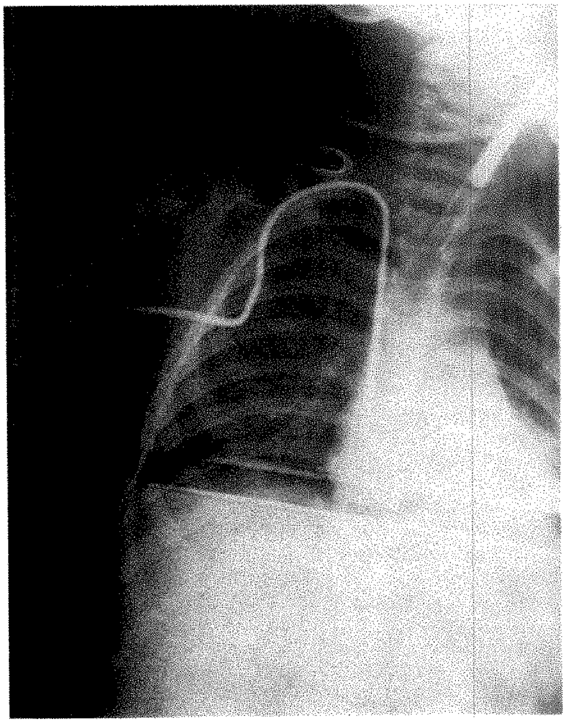

Fig. 3. The Hickman catheter inserted through the right internal jugular vein in a 3-year-old child.

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* The Royal Marsden Hospital and The Institute of Cancer Research, Sutton, Surrey.

unless satisfactory. The catheter should be fixed to the skin at the exit site to prevent accidental removal until the Dacron cuff is invaded by healing tissues. Daily catheter care consists of cleansing of the exit site and application of a sterile dressing.

In children below the age of 5 years the cephalic vein is too narrow to accept the diameter of this catheter and an alternative method of insertion into the internal jugular vein is used, similar to the method described for insertion of the Broviac catheter (Heinbach and Ivey, 1976). A small incision is made behind the posterior border of the sternocleidomastoid muscle immediately above the clavicle. The muscle is retracted anteriorly and the internal jugular vein is isolated between two stay sutures. A fine purse string suture is placed in the lateral wall of this vein and an appropriate length of Silastic tubing is threaded through a tiny venotomy. It is important that the subcutaneous tunnel enters the neck wound at its lateral extremity to allow as wide a sweep as possible before the catheter turns back on itself to enter the vein (*Fig.* 3). 'Hairpin' angulation in the neck will result in early catheter failure. The platysma is approximated with catgut sutures and the skin with fine nylon.

Results

Most of the patients in this series were children and young adults in remission from acute lymphoblastic or myeloblastic leukaemia who were being treated by total body irradiation and allograft bone-marrow reconstitution. Two patients with leukaemia were not in remission at the time of placement of the catheter. The series also includes 5 children with neuroblastoma being treated with high dose Melphalan, and 4 patients with complications of gastrointestinal malignancy.

Infective complications occurred twice in this series necessitating removal of the catheter. Both patients had acute myeloblastic leukaemia and neither was in remission. Both infections were associated with silk skin sutures used in one case to close the neck wound and in the other case to secure the catheter at the exit site. All the other catheters functioned normally without complication for 28–70 days (median time of 42 days) until they were removed at the end of treatment. Many patients were severely thrombocytopenic at the time of placement of the catheter and no complication from haemorrhage was seen, although platelet transfusion was given as a precaution immediately before surgery.

The catheter is removed by making a small incision over the Dacron cuff under local anaesthesia and dissection of the cuff from the surrounding tissues. Histological sections of the Dacron cuff after removal show dense infiltration of the interstices by fibrous tissue and abundant foreign body giant cells.

Discussion

The Hickman right atrial catheter has proved to be of great benefit in the management of patients requiring prolonged haematological and nutritional support, especially those undergoing bone-marrow transplantation. In this group of patients previous treatments have invariably thrombosed all peripheral veins and it is essential to be able to guarantee efficient access to the central circulation for the duration of parenteral support. Blood and blood product transfusions particularly predispose to clotting of cannulas, but at no time did a Hickman catheter thrombose despite frequent transfusions of whole blood, platelet and granulocyte packs, whole plasma, fresh frozen plasma, plasma protein fraction and salt-poor albumin. The catheter was used for total parenteral nutrition and to correct the frequent fluid and electrolyte imbalances associated with the treatment and complications of bone-marrow transplantation. For example, the intense diarrhoea of graft versus host disease and the distal renal tubular dysfunction associated with acute myeloid leukaemia, gentamicin and carbenicillin therapy required prompt correction. All antibiotics, cytotoxic agents and other necessary parenteral chemotherapy were administered via the catheter. Finally, the catheter was used for blood sampling and this was especially appreciated by the children, who were spared daily venopuncture. The facility to heparinize and seal the catheter is useful towards the end of treatment to allow children to play free of the encumbrances of giving-set and drip-stand and to allow both children and adults to leave hospital occasionally as condition permits.

In such a severely immune-suppressed group of patients, the benefits of this catheter must be weighed against the danger of infection. Patients with good peripheral veins who are likely to require haematological and nutritional support for a short time are better managed by other methods of cannulation. Patients with acute leukaemia who are not in remission probably have the greatest risk of infection, and the use of this semi-permanent catheter should be avoided until all other methods have been exhausted.

In this paper the use of the Hickman catheter is described only in the management of cancer, but its versatility allows it to be applied to other situations. It may be useful in paediatric non-malignant intensive care or in the management of patients with temporary gastrointestinal failure from such conditions as regional enteritis. The similar Broviac catheter has been described frequently as a permanent home hyperalimentation catheter (Broviac and Scribner, 1974; Broviac et al., 1975; Riella and Scribner, 1976), but the wider Hickman catheter is preferable in patients who require frequent blood and blood product transfusions.

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Thanks are due to Dr T. J. McElwain, Dr R. Powles and Dr H. Clink for allowing me to report cases admitted under their care. I am grateful to Dr R. O. Hickman, Department of Medicine, University of Washington, Seattle, Washington 98195, USA, for personal communications regarding the placement of this catheter. Thanks also go to Miss Lynn Baxter who typed the manuscript.

The Hickman catheter can be obtained from Evergreen Medical Products Inc., PO Box 296, Medina, Washington 98039, USA.

References

BROVIAC J. W., COLE J. J. and SCRIBNER B. H. (1975) A silicone rubber atrial catheter for prolonged parenteral alimentation. *Surg. Gynecol. Obstet.* **136**, 602–606.

BROVIAC J. W. and SCRIBNER B. H. (1974) Prolonged parenteral nutrition at home. *Surg. Gynecol. Obstet.* **139**, 24–28.

HEINBACH D. N. and IVEY T. D. (1976) Technique for placement of a permanent home hyper-alimentation catheter. *Surg. Gynecol. Obstet.* **143**, 634–636.

RIELLA M. C. and SCRIBNER B. H. (1976) Five years' experience with a right atrial catheter for prolonged parenteral nutrition at home. *Surg. Gynecol. Obstet.* **143**, 205–208.

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A suction cannulator for rapid peroperative cholangiography

A. M. HAY*

THE new instrument described here facilitates peroperative cholangiography and has particular advantages in the situation where cholecystectomy has been performed previously, where cystic duct identification and isolation are difficult, or where there is an awkward arrangement to the spiral valve of Heister.

Fig. 1 shows the suction cannulator in diagrammatic form. The principles underlying its design are as follows. The footpiece (A) is applied to the common bile duct and is held securely in place by suction (a standard operating theatre sucker is satisfactory) through channel (B). The device, held in this way, is not displaced by removal of packs or retractors. Gentle traction on the instrument separates the walls of the bile duct and thus produces a favourable configuration for insertion of a 23G × 25 mm needle through the needle guide (C) into the lumen of the bile duct. The length of the needle guide (C) is such that the needle cannot protrude from the footpiece by more than 4 mm. This distance has been found suitable for use in most sizes of duct, whether thin- or thick-walled. A small crimp in the needle guide grips the needle firmly. The expanded end of the needle guide ensures that the puncture site in the bile duct is not directly exposed to the suction force in the footpiece, and thus prevents excessive extravasation of bile or contrast medium.

Operation of the device is simple. The position and direction of the common bile duct are identified. It is best, though not essential, to clean off the covering peritoneum and fat so that the surgeon may be confident as to the alignment of the duct, and that no important structure, such as the hepatic artery, overlies the duct at the point where the device is to be applied. With suction connected and the needle, attached by suitably primed small-bore tubing to a syringe, lying loosely in the needle guide, the instrument is introduced into the wound. The suction channel serves as a convenient handle, the angle it makes with the footpiece facilitating placement high up under the liver if necessary. The footpiece is aligned with and applied to the duct. Once a suction seal has been obtained, the duct can be tented gently upwards and the cannulating needle pushed home in the needle guide. Aspiration of bile confirms a successful cannulation. After a little practice, it is possible to perform the whole procedure in just a few seconds.

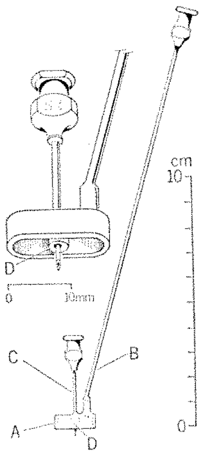

Fig. 1. Diagram of the suction cannulator: A, footpiece; B, suction channel and handle; C, needle guide; D, expanded end of needle guide.

The device has so far been used in 20 operations, satisfactory cholangiograms being obtained on 18 occasions. The device is not suitable for use, however, where there is a very narrow common bile duct; this was the cause of our 2 failures. Occasionally the bile duct may be a little distorted at the point of application of the device. This has not led to any errors of interpretation and may, in any case, be circumvented by the simple expedient of releasing suction and removing the device once the full volume of contrast medium intended for injection has been introduced into the biliary tree; the final X-ray film is then sure to be free of artefact.

The application of strong suction forces to the bile duct for periods of up to 10 min has not been associated with any detectable injury to that structure. Use of the fine needle has apparently prevented the development of annoying biliary leaks without providing any significant obstruction to the injection of contrast medium.

The new device, constructed in metal and plastic, is available in presterilized disposable form from Portex Ltd, Hythe, Kent.

Acknowledgements

The author wishes to express his gratitude to Messrs Derek Chappell and John Fearn of the Royal Postgraduate Medical School and to Mr David Cross of Portex Ltd for their expert technical assistance in the development of the suction cannulator. Mr Doig Simmonds of the Department of Medical Illustration, Royal Postgraduate Medical School, kindly provided the diagram.

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Book reviews

Modern Cardiac Surgery

D. B. Longmore. 240×160 mm. Pp. 393. Illustrated. 1978. Lancaster: MTP. £14·95.

THE course on cardiac surgery organized each year by the British Postgraduate Medical Federation has become an academic landmark on the calendar of all those who have a special interest in this subject.

This book is an up-to-date account of the growing edge of cardiac surgery as seen in April 1977 and covers many topics that are now becoming more clearly defined and better understood. Of particular interest today are the chapters on transplantation of the heart, mitral valve conservation, the preparation, preservation and use of tissue valves and the management of their complications. Frequent reference is made to echocardiography and one chapter is devoted to this subject. The section on elective cardiac arrest, myocardial preservation and left ventricular function is a useful appraisal of a subject which is still fraught with controversy and individual opinion.

The major emphasis is on the surgery of the more complicated forms of congenital heart disease. Here technical surgical procedures are described in detail with many excellent illustrations. Complications, snags and even failures are discussed in a way that is not possible in the journals or a standard textbook.

This book will be a valuable record for those who attended the course in 1977 and a useful reference for others. It is not a book that one would wish to read from cover to cover but each chapter reads easily, indicating considerable revision of the spoken word. If this book is kept alongside the published proceedings of earlier and subsequent conferences, a useful shelf on fashions and trends in cardiac surgery will soon be established.

J. W. JACKSON

Sémiologie Chirurgicale

Professor L. Leger et al. Fourth edition. 280×215 mm. Pp. 503 +xiii. Illustrated. 1978. Paris: Masson. No price given.

IT is a pleasure to review the fourth edition of *Sémiologie Chirurgicale* by Professor Lucien Leger and his colleagues. It has been translated into German, Spanish, Italian, Iranian, Japanese and Turkish, which speaks highly of its format as a primer in surgical practice for the undergraduate and postgraduate.

The line drawings are full of Gallic wit, each making its point dramatically, often very amusingly. The X-rays are good and to the point. It is profusely illustrated in black and white. It is a shorter edition of Bailey and Love and is in a similar way didactic but orthodox. It is essential reading for anyone wishing to gain a rapid knowledge of French medical terminology. It can be highly recommended.

J.-C. GAZET

Amputation and Prostheses

M. Vitali, K. P. Robinson, R. G. Andrews and E. E. Harris. 245×185 mm. Pp. 241+ix, with 167 illustrations. 1978. London: Baillière Tindall. £10·50.

THIS work is directed primarily at the young surgeon in training. It contains enough technical information to guide him through all but the most obscure levels of amputation. The book covers in considerable detail the important matters of preoperative assessment and selection of level, with due regard to the prosthetic implications. Postoperative care and rehabilitation are dealt with adequately and there is a unique survey of modern British prosthetic practice.

This is a clearly written and polished work encompassing several disciplines. It is likely to be read with interest by all those involved in the care of amputees, whether they be new to the field or old hands.

J. C. ANGEL

Surgical Conditions in Paediatrics

H. Homewood Nixon. 216×138 mm. Pp. 448. Illustrated. 1978. Sevenoaks: Butterworths. £23·00.

THE author, in his preface, indicates that this book was written mainly for medical paediatricians. Nevertheless, it is an invaluable book for general surgeons, who still, as he points out, carry out most of the ordinary surgery of children. The book deals in detail with diagnosis, differential diagnosis and management, just those areas where the general surgeon feels himself at a disadvantage when cooperating with his medical paediatric colleagues. The place of surgery in the overall management, the choice of operation, its timing and problems of pre- and postoperative care are most fully discussed. There is no step-by-step description of operations but there are many helpful and illuminating details of operative technique—sufficient to make a surgeon wish that this aspect had been developed more fully. This is one of the new medical books that could be wished longer. Nevertheless it is churlish to complain where so much has been provided. The book covers the whole field of paediatric surgery with the exception of orthopaedics. It is lucidly written, purposefully illustrated and garnished with well-chosen references, benefiting greatly from being written by one man with the authority of long personal experience and eminence in this specialty. Despite the somewhat startling price, the book is to be recommended for any surgeon dealing with children.

A. CAMERON

Transurethral Resection

Professor J. Blandy. Second edition. 250×190 mm. Pp. 184+vii. Illustrated. 1978. Tunbridge Wells: Pitman Medical. £14·00.

IT is always a pleasure to read the works of Professor John Blandy, and this new edition of *Transurethral Resection* is no exception. Throughout, the text is easy to read and the illustrations by the author's hand are succinct and clear. Opening with a brief historical review, the author clearly covers the current instruments and equipment, and explains, in simple language, their workings. The indications for transurethral resection are carefully explained. There now follows a superb description of basic resection skills, and then an exciting description of how the author himself resects a benign prostate. He describes shamelessly all the pitfalls and how to get out of them. An acknowledgement of, and the technique employed in, bladder-neck incision is somewhat thin. As this book is on transurethral resection, the techniques for resecting bladder tumours are described. A brief description of the author's preferences for managing bladder tumours is outlined. The management of the larger solid tumours, T3 and 4, is unfortunately lumped together, and it would appear that the same treatment applies to both. Likewise, the impression is given that in the combined management of T3 bladder tumours by radiotherapy and surgery, it is preferable to employ 6000 rad, as opposed to 4000 rad, in the preoperative period; this is, of course, not the modern teaching. The author, quite correctly, covers the coexistence of bladder stones and the management of these in combination with bladder neck obstruction. The book finishes with a description of the all-important postoperative care and complications, early and late. It is surprising that urea levels are measured in milligrams per cent, and also to learn that the Kidd–Riches big ball diathermy cystoscope is now obsolete!

This is a masterful description of Professor Blandy's techniques, which have aided and abetted many past and present RSOs both at St Peter's and the London Hospital. It is clearly complementary to other books on the subject, and will be avidly read, not only by trainee resectionists but by all who practise this technique.

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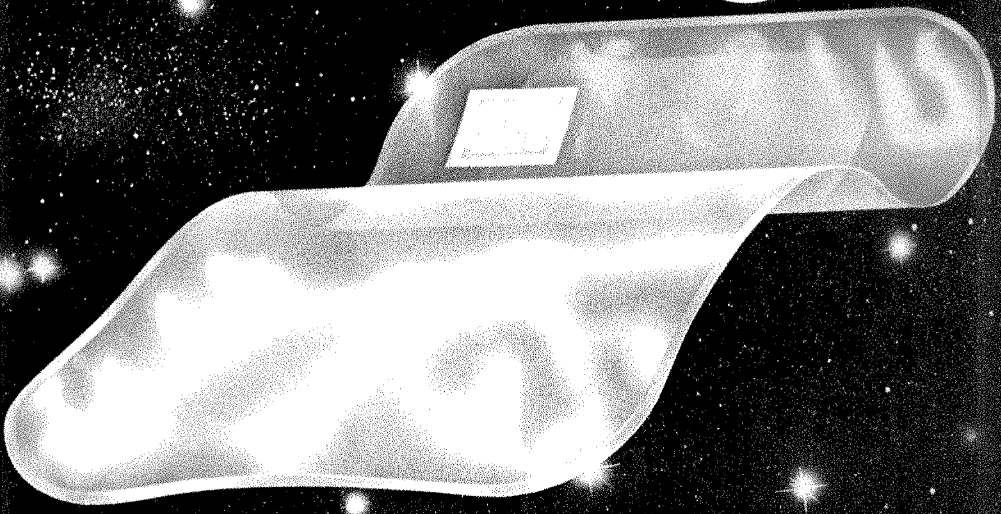

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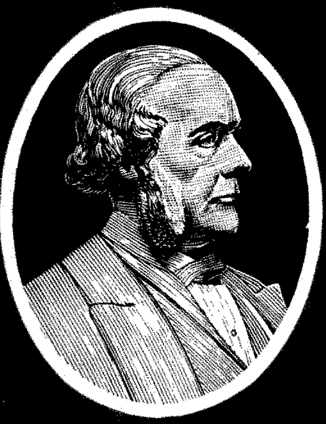

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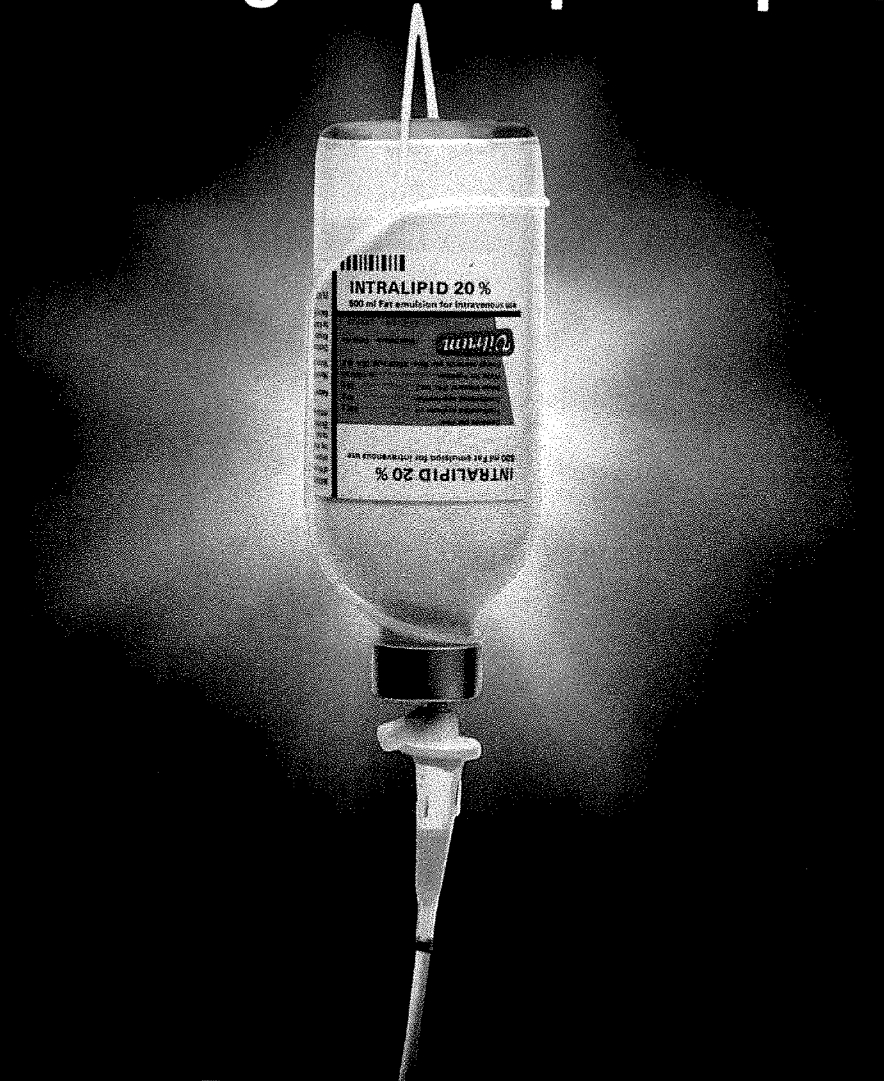
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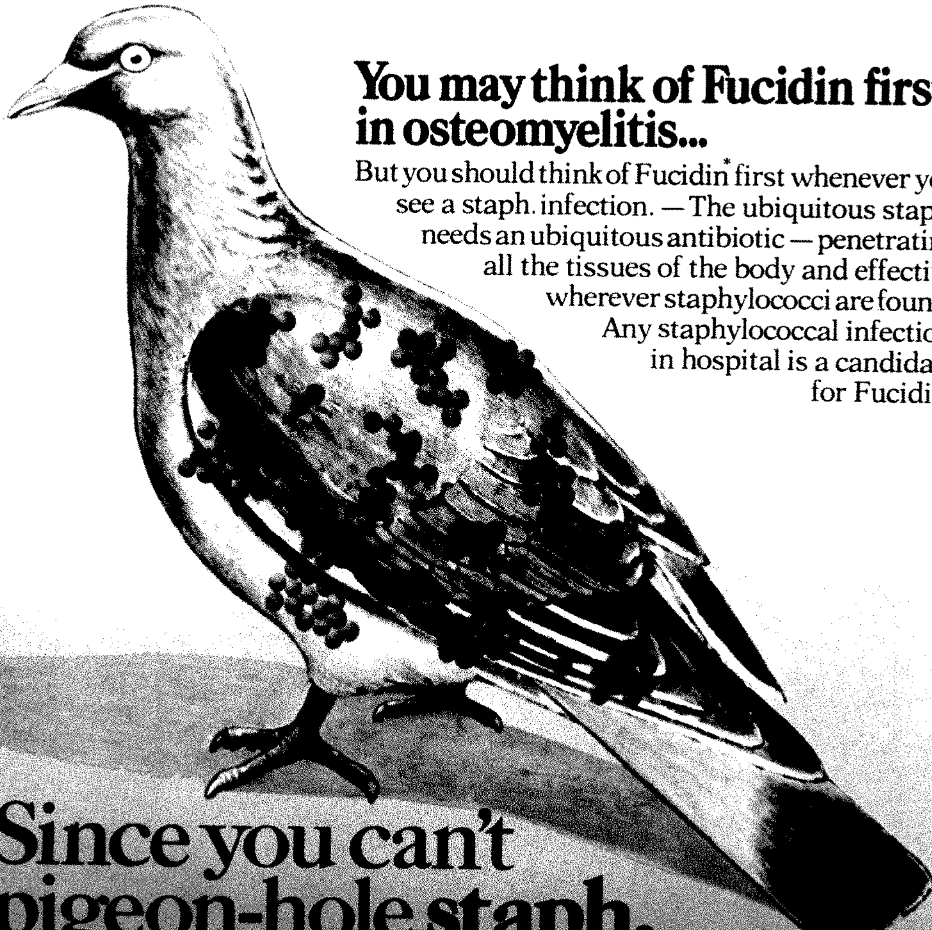

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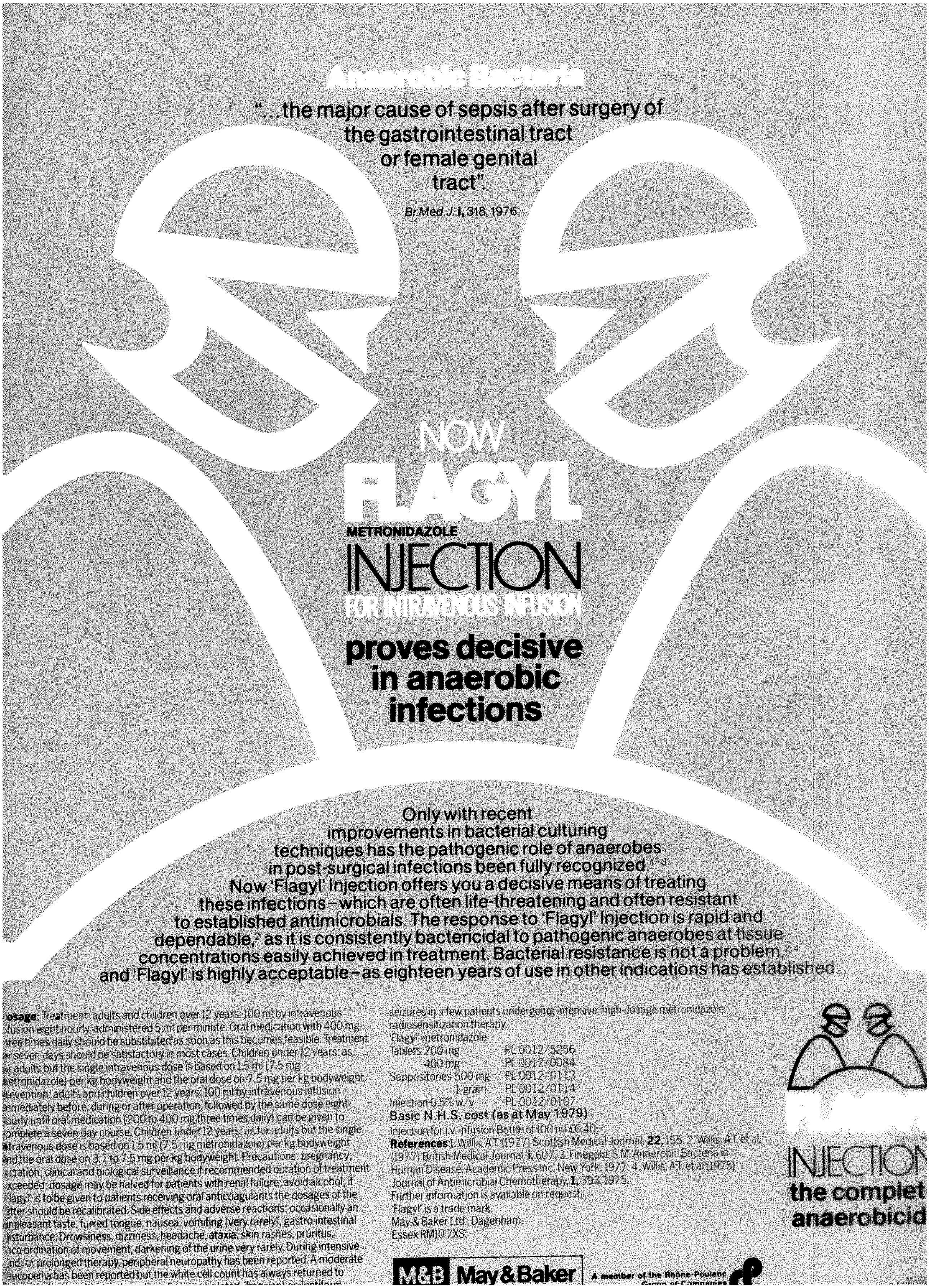
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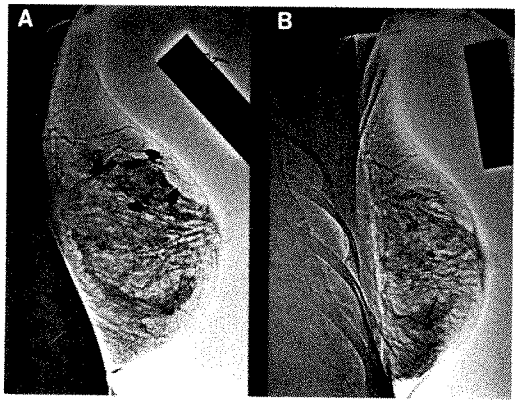

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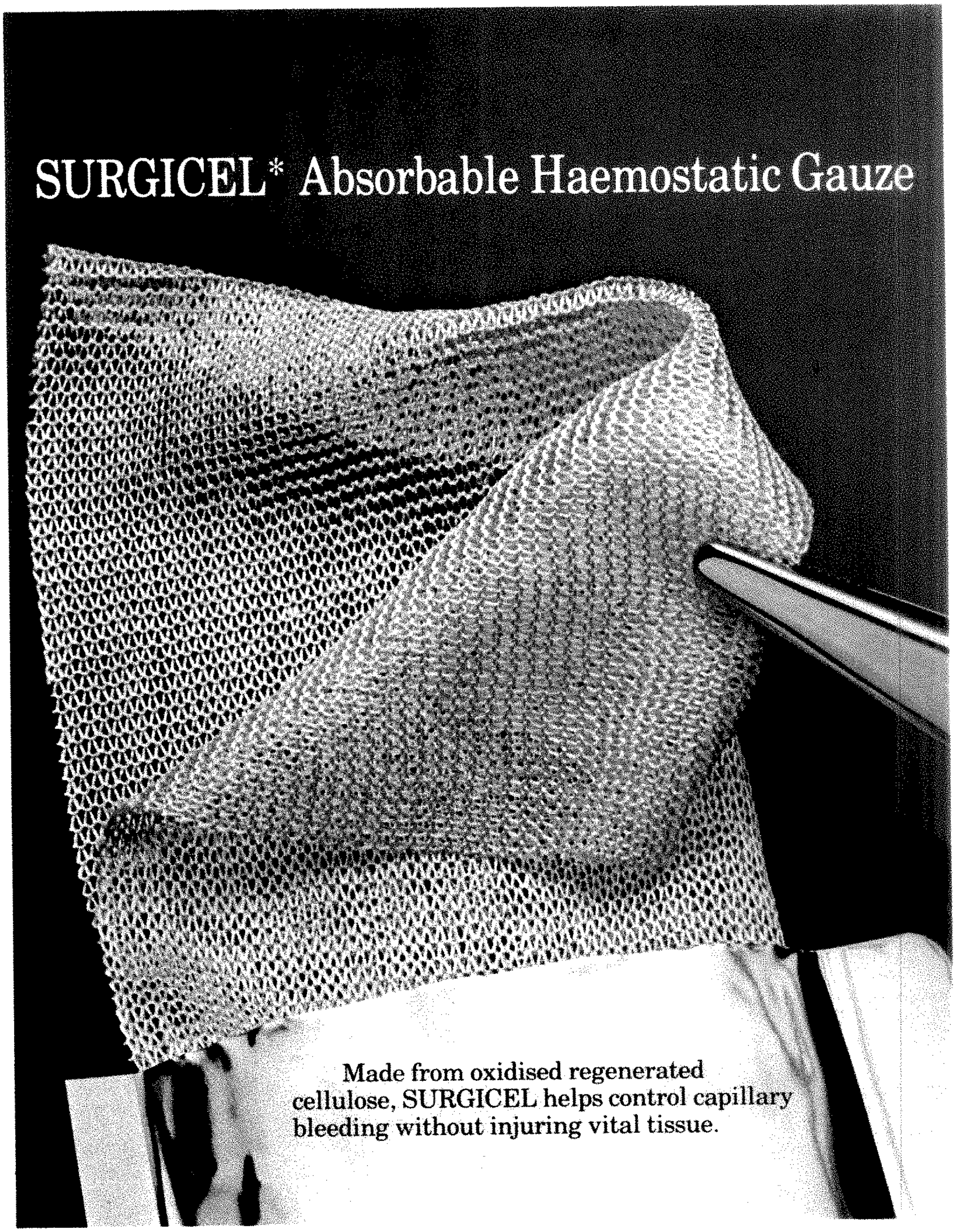
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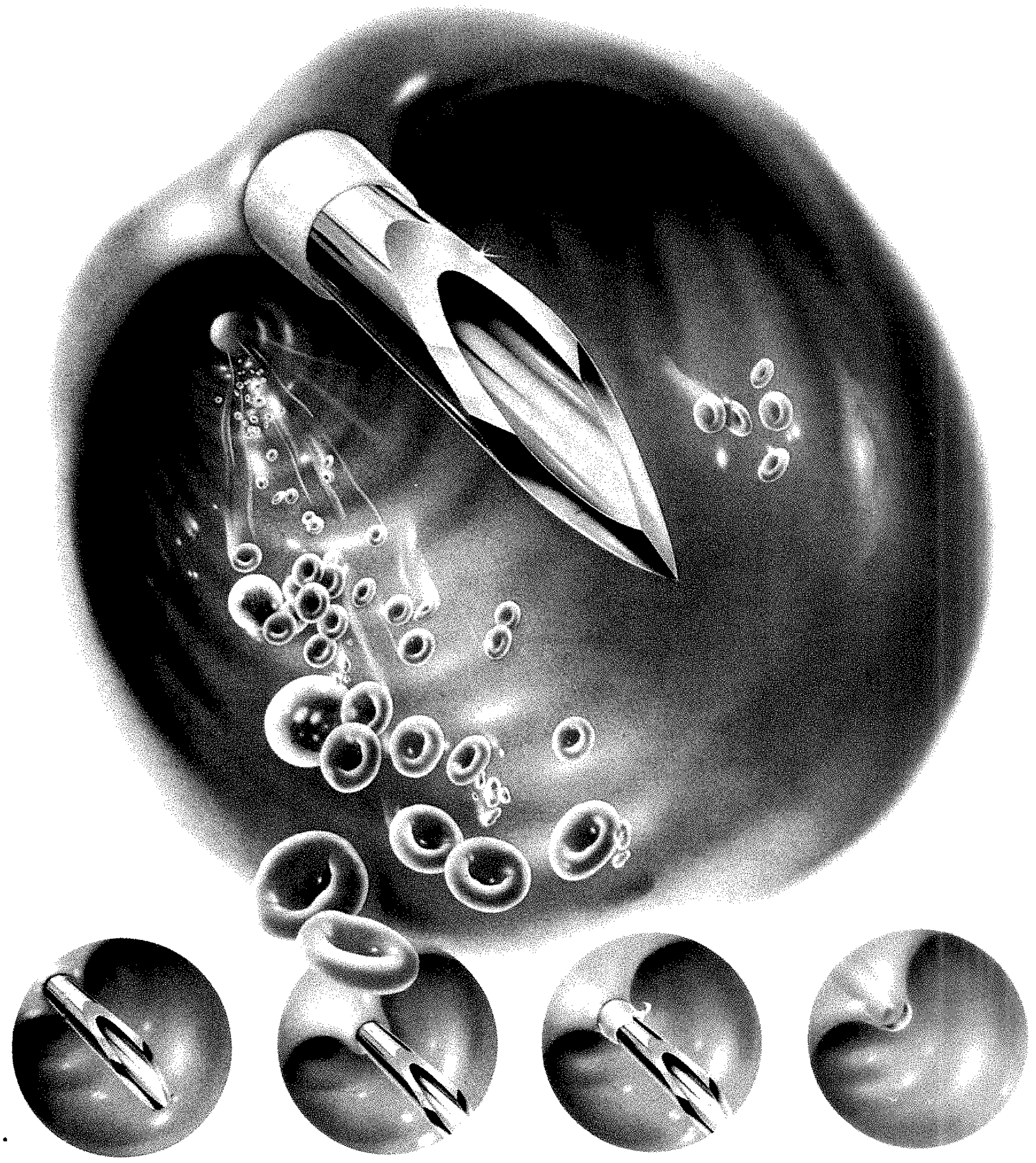

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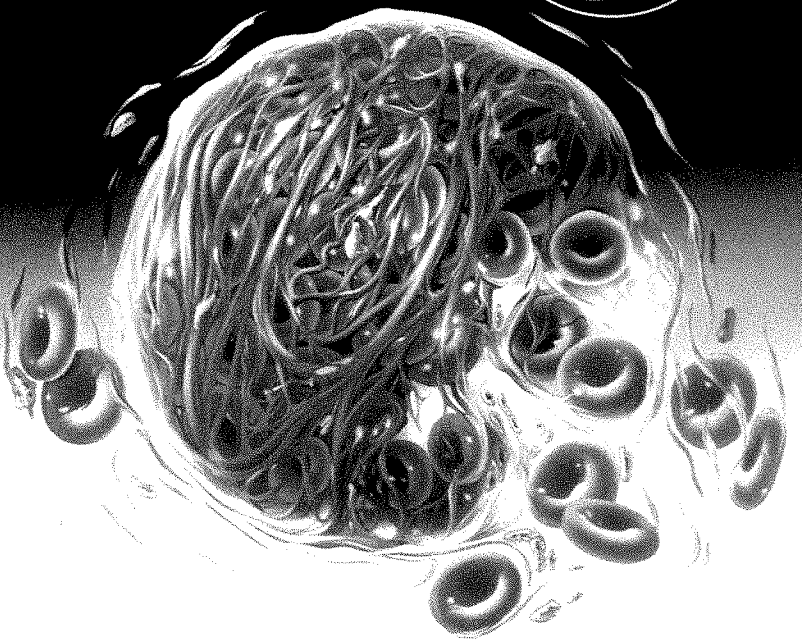

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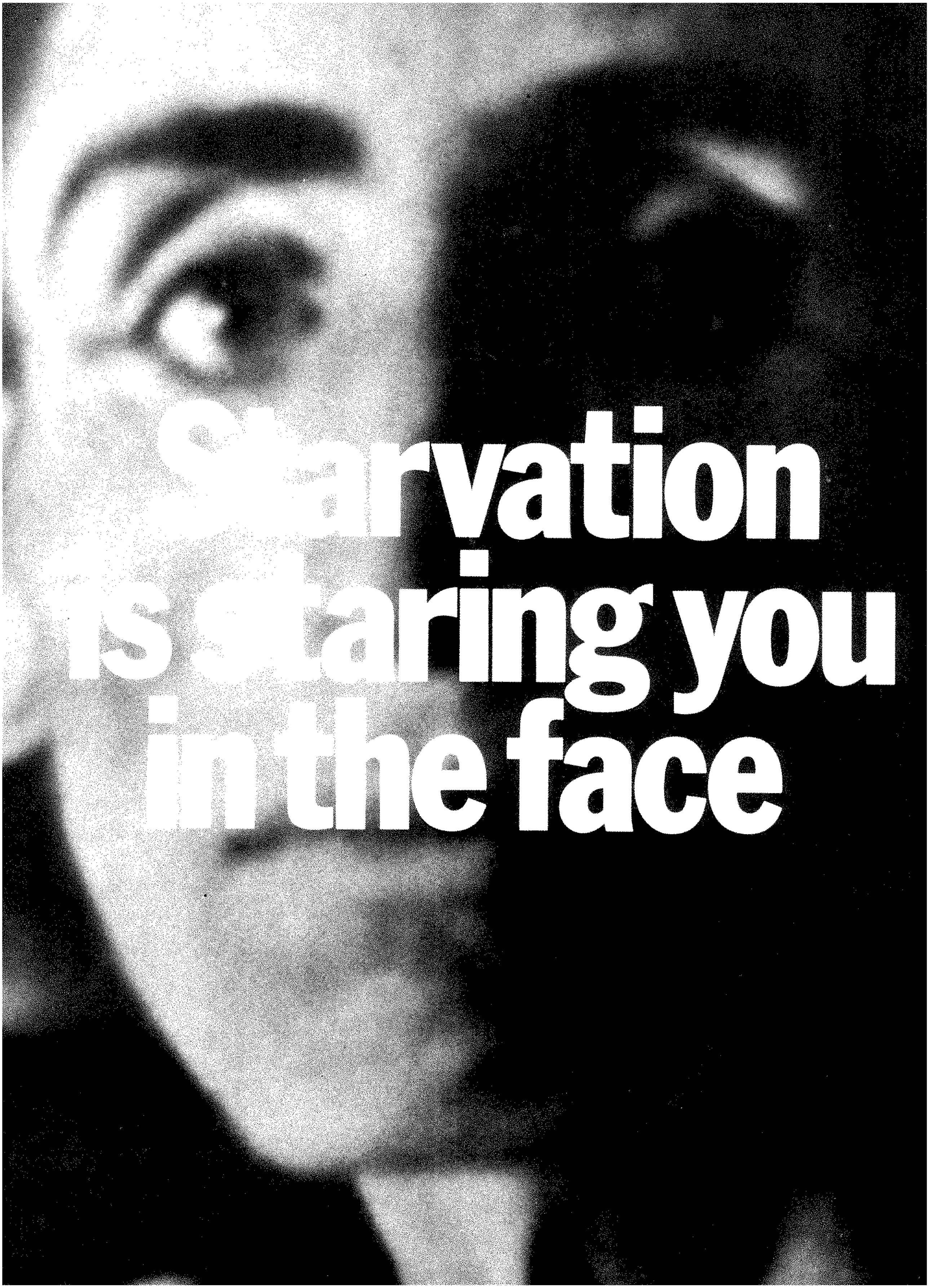
Data sheet information **Presentation** Abbokinase is available in 10ml vials containing 250,000iu of a highly purified sterile lyophilised formulation of urokinase obtained from cultures of human kidney cells. Urokinase plasminogen activator excreted in the urine of normal healthy individuals. When reconstituted with 5.2ml distilled water according to directions each ml of isotonic solution will contain 50,000iu urokinase 5mg mannitol 9mg sodium chloride. **Uses** Abbokinase in vivo and in vitro produces the release of plasmin by an enzymatic action on human plasminogen. Abbokinase has only minimal activity in reducing fibrinogen levels but bloo plasminogen levels are reduced, the effect being dose-dependent. Abbokinase is virtually non-antigenic to humans and, in therapeutic doses, is thromboplastin-free. Thrombolytic therapy is indicated in the treatment vascular occlusions caused by forming or recently formed fibrin clots. Theoretically the best results will be obtained with thrombi less than 24 hours old. Abbokinase is indicated as a thrombolytic agent in pulmona embolism **Dosage and Administration** Abbokinase is administered intravenously by continuous infusion, usually for a period of 12 hours. It is recommended that Abbokinase be given in a solution of Normal Saline by consta infusion. An initial loading dose to be given during the first ten minutes of therapy is advocated. This loading dose should be equal to the amount which it is planned to administer over each succeeding period of one hour. Ideal an infusion pump should be used to maintain a constant rate of infusion. Abbokinase is reconstituted with 5.2ml sterile water for injection, without preservatives. For administration the reconstituted solution should be furth diluted with normal saline to the total volume of solution (195ml) for a 12 hour treatment including the priming dose. From this solution, 15ml are given over a period of 10 minutes as the priming dose and the remainder ove period of 12 hours at the rate of 15ml/hour. Dosage: It should be noted that patient-to-patient variation in response can be expected, due to individual variation in levels on inhibitory factors. Certain disease states such uraemia, some malignancies and dyslipidaemias can be associated with an increased plasma level of urokinase or plasmin inhibitors. In other conditions such as massive pulmonary embolism, endogenous fibrinolyt activity may be increased. The recommended dosage regimen for the treatment of pulmonary embolism is: Loading dose 4,400iu per kg bodyweight over 10 minutes. Constant infusion dose 4,400iu per kg bodyweight p hour. Duration of infusion, 12 hours. **Contra-indications, Warnings, etc.** Contra-indications Manifest or recent (i.e. within 3 days) haemorrhage. Any haemorrhagic diathesis. Severe hypertension. During cardiopulmona resuscitation. During pregnancy or suspected pregnancy. Warnings and Precautions The major adverse effect of Abbokinase is haemorrhage, usually associated with too high dosage. A high incidence of bleeding fro minor skin lesions, therapeutic and diagnostic puncture sites and pre-existing gastro-intestinal lesions has been observed with high dosages. Any evidence of significant internal bleeding necessitates the cessation thrombolytic therapy. An anti-fibrinolytic agent such as epsilonaminocaproic acid (EACA) may be used as an antidote if required. Epsilonaminocaproic acid should be available for use, if necessary, during infusions wi Abbokinase when high doses are being administered. Post-partum for one month. Recent surgery (within 3 days). Concurrent anti-coagulant therapy should be administered cautiously. Mild temperature increases have been observed during thrombolytic therapy with Abbokinase. When there is a history of hypersensitivity to drugs etc., caution is advised and facilities as well as corticosteroids, adrenaline, etc. should be readily available when Abbokinase is infused. Monitoring The monitoring of fibrinolytic activity and of plasminogen levels is desirable. Pharmaceutical Precautions: The lyophilised powder should be stored at 2-8°C. Reconstituted solution should be used immediately after mixing and secondary dilution. **Legal Category** POM **Package Quantities** Available in packs of 2 vials of 250,000iu each (List No. 6109). **Further Information** The potency of Abbokinase is expressed in International Units (iu). For practical purposes the iu is considered by most authorities to be equivalent to the CTA unit. The Ploug unit is usually considered to be equal to 1.4iu. **Product Licence Number** 0037/0096 **References** 1. Kakkar VV, Scully MF. Thrombolytic therapy. *Brit Med. Bull.* **34(2)**: 191–199, 1978. 2. Kakkar VV, Scully MF. *Op. cit.*, p192. 3. Genton E, Claman HN. Urokinase antigenic studies in patients following thrombolytic therapy. *J Lab Clin Med* **15**: 619, 1970. 4. Urokinase Pulmonary Embolism Trial. Phase I results: a cooperative study. *JAMA* **214**: 2163, 1970. 5. Urokinase Pulmonary Embolism Trial Study Group. Urokinase-streptokinase Embolism Trial. *JAMA* **229**: 1606, 1974. Further information available on request from Abbott Laboratories Limited, Queenborough, Kent ME11 5EL. ® Registered Trade Mark of Abbott Laboratories Ltd. AK389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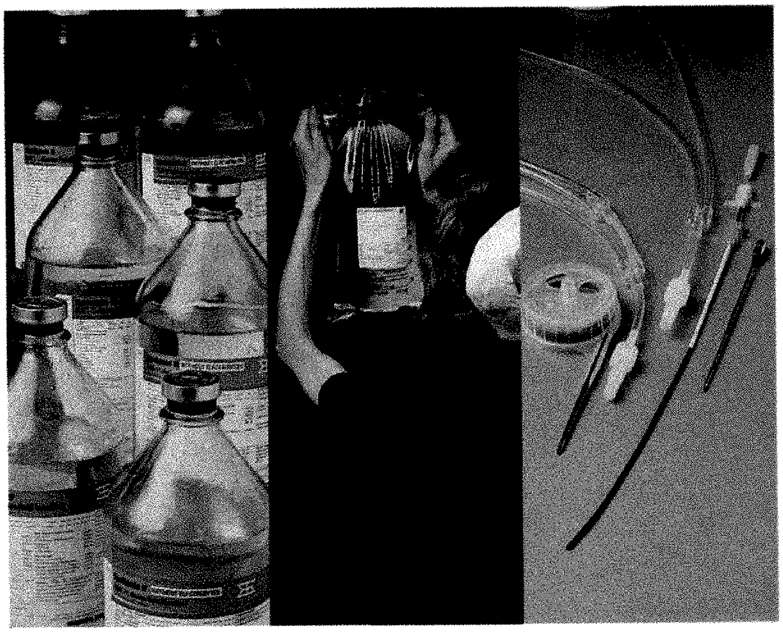

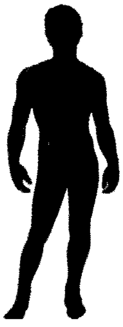

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Presentation
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Synthamin 17 without electrolytes (PL 0116/0069) 500ml £9.45.

Reference
1. Powell-Tuck, J., Farwell, J.A., Nielsen, T. and Lennard-Jones, J.E. (1978). Team approach to long-term intravenous feeding in patients with gastrointestinal disorders. Lancet, **ii,** 825-828.

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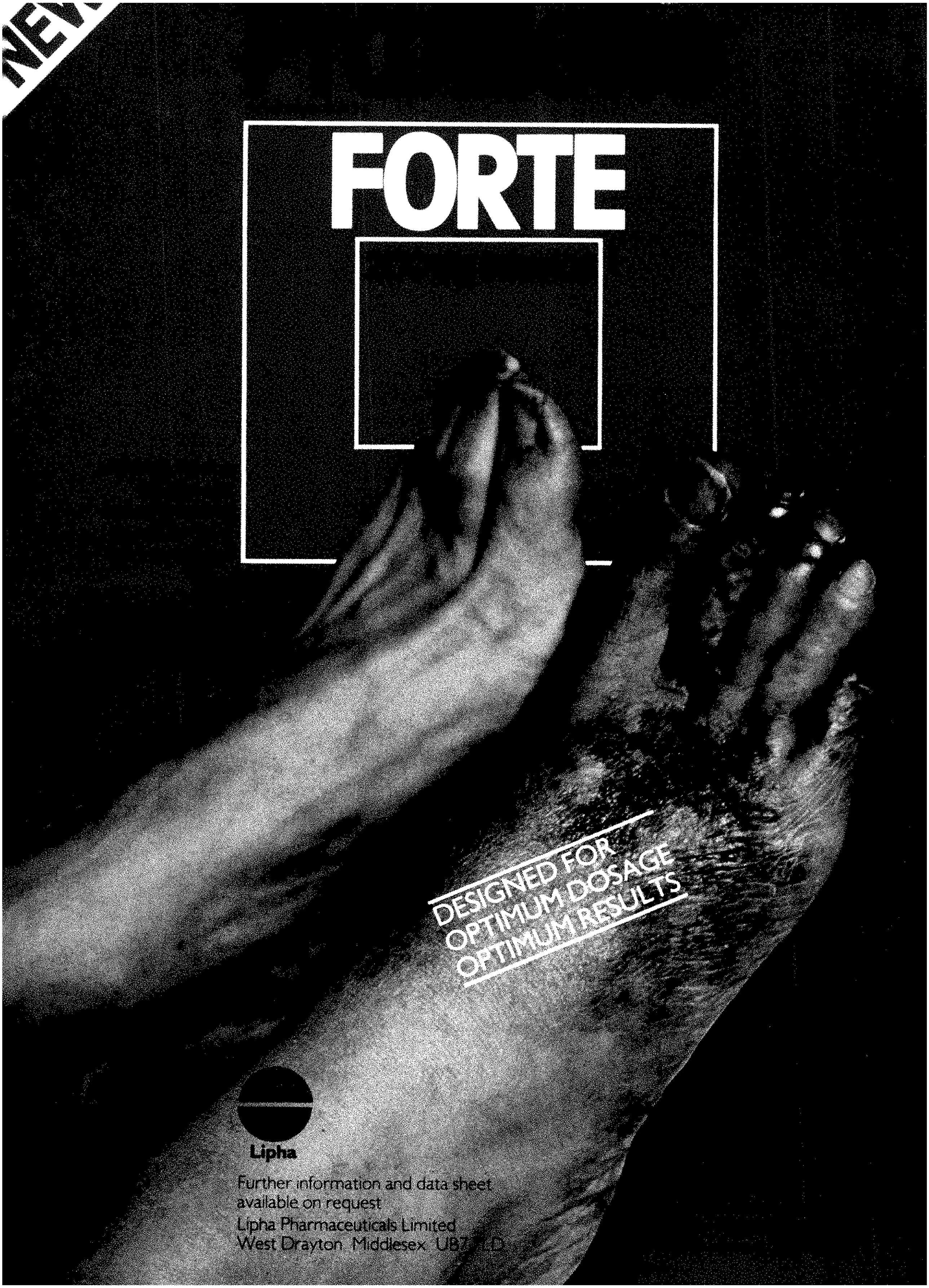

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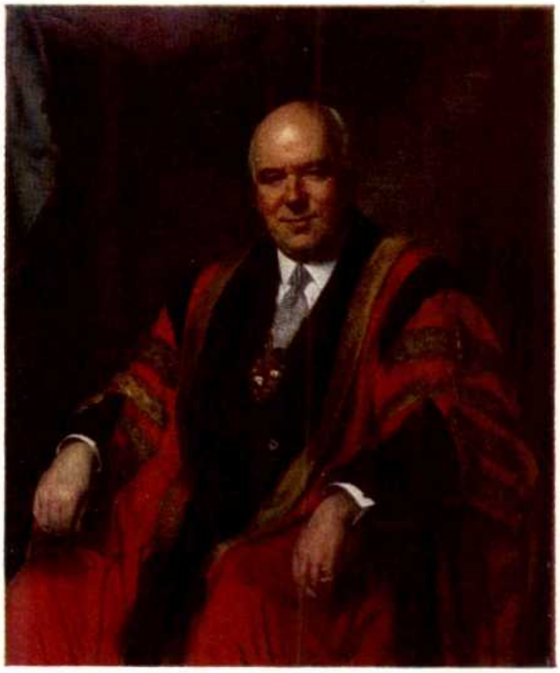

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In grateful memory

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ASSOCIATION OF SURGEONS OF GREAT BRITAIN AND IRELAND

The Annual Meeting of the Association took place in Norwich on 4, 5 and 6 April 1979, with the President, Mr A. B. Birt, CBE, FRCS, in the Chair.

SHORT PAPERS FOR THE MOYNIHAN PRIZE AND MEDAL

[The prize was awarded to Mr C. N. McCollum (St James's University Hospital, Leeds) for his paper 'The value of measuring intravascular platelet aggregates in the prediction of postoperative pulmonary dysfunction'.]

Blood transfusion and renal transplantation

G. PROUD, B. K. SHENTON AND B. M. SMITH*

SUMMARY

Blood transfusions given to potential renal transplant recipients are beneficial to subsequent graft survival. This study has shown an association between the inhibitory activity of patients' plasma on their own non-specific lymphocyte responses to antigen and the administration of blood transfusions. Most of the inhibitory activity was related to alpha-2 macroglobulin. Alpha-2 macroglobulin was able to prolong the survival of rat cardiac allografts. Immunoregulatory activity related to the alpha globulins of plasma has been described in a wide variety of conditions (i.e. cancer, pregnancy, diabetes) and this study has shown similar activity following blood transfusions.

REPORTS from Los Angeles (Opelz et al., 1973) and Newcastle (Murray et al., 1974) first drew attention to the possible beneficial effects on renal transplant recipients of blood transfusions administered prior to transplantation. Since then, most transplantation centres throughout the world have found an association between blood transfusions given before transplantation and improved graft survival. Uldall et al. (1977) updated the Newcastle results and confirmed the original findings of improved graft survival when blood transfusions had been given prior to transplantation.

The latest analysis of our results in 274 consecutive first cadaver allografts performed between October 1969 and December 1977 is shown in *Fig.* 1. The results were analysed by comparing renal transplant recipients who had received blood transfusions prior to transplantation, with those who had not, in two ways. First, all graft failures were included, and then non-immunological failures were excluded. The results were assessed by the actuarial method of Barnes (1965). Regardless of whether non-immunological failures were excluded or not, those patients who had received blood transfusions prior to transplantation were at less risk from graft loss than non-transfused patients. The improved graft survival was still apparent at the 6-year follow-up in the transfused patients, though at this stage only a comparatively few patients were under review and statistical significance between the groups was no longer apparent.

A median of 5 units of whole blood or packed cells had been transfused to the patients studied. The amount of blood transfused had no effect on subsequent graft survival, two or three units having the same effect as many.

The reasons for improved graft survival following transfusion are not known (Perkins, 1977; Persijn et al., 1977). We have studied *in vitro* the ability of plasma to regulate non-specific lymphocyte reactions with antigen, and have identified some of the plasma factors which may be responsible for the transfusion-induced suppression.

Patients and methods

Four patient groups were studied: (i) normal subjects—non-transfused (normal); (ii) renal failure patients—non-transfused (renal 0); (iii) renal failure patients—multi(10)-transfused (renal multi) and (iv) haemophiliacs—multi(10)-transfused (haemophiliacs).

Renal patients had never been transplanted, and all required dialysis. Transfused renal patients had been on dialysis for a longer period than non-transfused patients. Fehrman et al. (1978) report that improved graft survival is linked more strongly to pre-transplant dialysis than to blood transfusion. To control any possible immunological effects of dialysis a group of multi-transfused haemophiliac patients was also studied.

The non-specific lymphocyte inhibitory activity of plasma was studied by measuring the ability of each patient's plasma to inhibit the response of both allogeneic and autologous lymphocytes to PPD antigen (purified protein derivative of mycobacterium tuberculosis). The inhibitory activity of plasma was measured using the tanned erythrocyte electrophoretic mobility (TEEM) test (Shenton et al., 1978). This is an electrophoretic technique for measuring changes in cell-mediated immune responses and depends upon the production of a lymphokine from stimulated lymphocytes, termed electrophoretic slowing factor, which reduces the mobility of tanned sheep red blood cells in an electrophoretic field. The lymphokine alters the surface electrical charge on the tanned sheep red cells and thus alters their mobility when this is measured in the electric field of a Zeiss cytopherometer. Test plasma samples were diluted (1/60, 1/120, 1/140 etc.) in Hanks's balanced salt solution, and the dilution of plasma producing 50 per cent inhibition of the lymphocyte response to PPD (determined from graphically expressed results) was taken as a standard. All tests were performed on fresh plasma, which was obtained from heparinized venous blood. The ability of each plasma to inhibit the response of lymphocytes to PPD was measured against both allogeneic lymphocytes, obtained from normal adult volunteers, and autologous lymphocytes from the patient's own blood.

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* Department of Surgery, University of Newcastle-upon-Tyne.

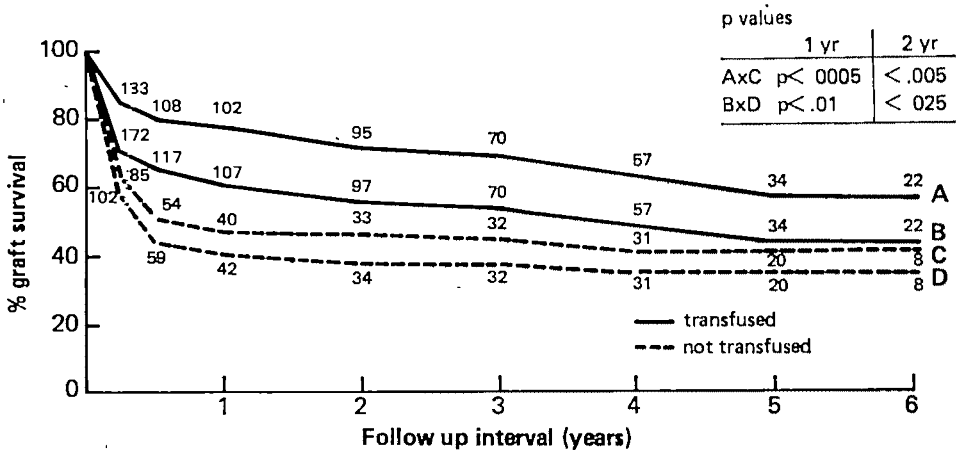

Fig. 1. Effect of prior blood transfusion on 274 consecutive first cadaver renal allografts (including 56 non-immunological failures). A+C: non-immunological failures excluded; B+D: all failures.

Lymphocytes were obtained from peripheral blood by the one-stage sodium metrizoate technique, 'Lymphoprep' (Bøyum, 1968) and were thoroughly washed three times in Hanks's balanced salt solution before use. The lymphocytotoxicity of each plasma sample was assessed on allogeneic lymphocytes by the method described by Dewar and Murray (1976) and on the lymphocytes used in the test.

Statistical methods

The inhibitory activity of plasma and plasma fractions on lymphocyte responses to antigen (*Tables I, II* and *III*) was compared between groups using Student's *t* test analysis, and the same test was used for comparing plasma alpha-2 macroglobulin concentration (*Table IV*). Cardiac allograft survival following macroglobulin therapy (*Table V*) was evaluated using Student's *t* test analysis as shown, and was also studied using the non-parametric rank test of Wilcoxon when the statistical significance between groups was the same as with the *t* test. Renal graft survival was assessed by the actuarial method of Barnes (1965).

Results

Inhibitory activity of whole plasma

The concentrations and dilutions of plasma producing 50 per cent inhibition of the lymphocyte response to antigen are shown in *Table I*. In renal patients, the inhibitory activity of plasma from transfused patients against allogeneic lymphocytes was much greater than plasma from non-transfused patients, 50 per cent inhibition of the lymphocyte responses occurring at a dilution of 1/1470 compared with 1/119 in the non-transfused patients ($P<0·01$). Similarly, the inhibitory activity of plasma from haemophiliacs was much greater (50 per cent inhibition occurring at a plasma dilution of 1/1170) compared with normal subjects (1/75; $P<0·01$). There was no difference in the inhibitory activity on allogeneic lymphocytes of plasma from each transfused group ($P=0·112$). Equally, there was a significant rise in the inhibitory activity of plasma against autologous lymphocytes in the transfused patients (renal multi—50 per cent inhibition occurred at a dilution of 1/556 compared with renal 0—1/119, $P<0·01$; and haemophiliacs—1/849 compared with normal—1/93, $P<0·01$). Haemophiliac patients showed greater autologous lymphocyte inhibitory activity than transfused renal patients, suggesting that the inhibitory activity was more likely to be due to transfusion than some effect of dialysis.

Table I: CONCENTRATIONS AND DILUTIONS OF PLASMA PRODUCING 50 PER CENT INHIBITION OF LYMPHOCYTE RESPONSES TO ANTIGEN

Plasma group	Test lymphocytes	50% inhibition Conc. (10^{-3})	Dilution	s.d.$\pm(10^{-3})$
Normal	(a) Allo ($n=10$)	13·34	1/75	0·39
	(b) Auto ($n=5$)	10·7	1/93	1·6
Renal 0	(c) Allo ($n=12$)	8·4	1/119	1·39
	(d) Auto ($n=5$)	4·9	1/204	0·38
Renal multi	(e) Allo ($n=11$)	0·7	1/1470	0·22
	(f) Auto ($n=7$)	1·8	1/556	0·32
Haemophiliacs	(g) Allo ($n=10$)	0·85	1/1170	0·27
	(h) Auto ($n=6$)	1·18	1/847	0·26

t test analysis:	Allo	Auto
	a *v*. g: $P<0·01$	b *v*. h: $P<0·01$
	c *v*. e: $P<0·01$	d *v*. f: $P<0·01$
	e *v*. g: $P=0·112$ (n.s.)	f *v*. h: $P<0·05$

Allo, allogeneic, Auto, autologous.

Inhibitory activity of fractionated plasma

To study the fractions of plasma responsible for the raised lymphocyte inhibitory activity, 2-ml plasma samples were subjected to gel filtration on G200 Sephadex (Ford et al., 1973). The column used was 1 × 30 cm and the running buffer 0·01 M phosphate buffered saline, pH 7·2, set at a flow rate of 18 ml/h. The protein concentration of the eluted fractions was determined spectrophotometrically (280 nm absorption using the Uvicord LKB analyser) and the pattern of protein elution was identified with fused rocket electrophoresis (Weeke, 1973). The antibody to

Table II: SUMMARY OF DILUTIONS OF POOLED PLASMA FRACTIONS PRODUCING 50 PER CENT INHIBITION OF LYMPHOCYTE RESPONSE TO ANTIGEN

		Macroglobulins (peak 1)		γ-globulins (peak 2)		Albumin (peak 3)		Low molecular weight (peak 4)	
Plasma group	*n*	A	B	A	B	A	B	A	B
Normal	4	1/104	1/81	—	—	—	—	—	—
Renal 0	4	1/135	1/68	—	—	—	—	1/77	1/70
Renal multi	4	1/309*	1/303*	—	1/86	—	—	1/201*	1/193*
Haemophiliac	4	1/500†	1/435†	—	1/143	—	—	—	—

Lymphocytes: A = autologous, B = allogeneic.
Where no values are given, no activity was detected at 1/60 dilution.
t test analysis: * $P<0{\cdot}01$ comparing renal-multi with renal 0. † $P<0{\cdot}01$ comparing haemophiliacs with normal.

Table III: CONCENTRATION* OF PLASMA PRODUCING 50 PER CENT INHIBITION OF ALLOGENEIC AND AUTOLOGOUS LYMPHOCYTE RESPONSES TO ANTIGEN BEFORE AND AFTER IMMUNO-ADSORBENT CHROMATOGRAPHY

Plasma group	*n*	Pre column	Post anti-α2M column	Post control column
Allogeneic				
Normal	4	15·04±3·1 (1/66)	—	13·5±1·05 (1/74)
Renal 0	4	10·0±0·3 (1/100)	19·6±2·8 (1/51)†	14·7±2·83 (1/68)
Renal multi	4	0·62±0·05 (1/1512)	2·3±0·05 (1/421)†	0·567±0·02 (1/1763)
Haemophiliacs	4	0·585±0·026 (1/1709)	2·9±0·2 (1/344)†	0·797±0·08 (1/1254)
Autologous				
Normal	4	9·55±2·71 (1/105)	—	15±3·75 (1/67)
Renal 0	4	6·6±1·42 (1/151)	17·4±4·7 (1/57)†	7±0·62 (1/142)
Renal multi	4	1·54±0·54 (1/649)	5·85±0·43 (1/171)†	1·59±0·19 (1/629)
Haemophiliacs	4	1·37±0·2 (1/727)	—	1·19±0·2 (1/840)

* Concentration: $\times 10^{-3} \pm 1$ s.d. $(\times 10^{-3})$ (and dilution).
† $P<0{\cdot}01$ compared with pre-column values.
Where no values are given, no activity was detected at 1/40 dilution.

Table IV: α2M CONCENTRATION

Plasma group	*n*	Conc. (mg/100 ml plasma)	±1 s.d.
Normal	15	282·1	46·4
Renal 0	14	261·9	62·8
Renal multi	12	274·4	78·3
Haemophiliacs	16	383·2*	148·4

* $P<0{\cdot}05$ compared with each other group.

Table V: MACROGLOBULIN EFFECT ON RAT CARDIAC ALLOGRAFT SURVIVAL

	n	Graft survival (d)	±1 s.d. (d)
Untreated control rats (a)	17	7·3	0·47
Macroglobulin-treated rats (b)	9	10·6	1·67
Albumin-treated rats (c)	5	7·2	0·44

t test analysis: a *v.* b $P<0{\cdot}01$; b *v.* c $P<0{\cdot}01$.

human plasma proteins was prepared in the rabbit and supplied by Mercia Diagnostics Limited. Eluted fractions were collected and pooled into four aliquots according to the main protein peaks (Ford et al., 1973): peak 1 (macroglobulins); peak 2 (γ-globulin); peak 3 (albumin); peak 4 (low molecular weight). The inhibitory activity of each pooled aliquot was determined using both allogeneic and autologous lymphocytes. A summary of the inhibitory activity is shown in *Table II*. In normal subjects all the lymphocyte inhibitory activity was confined to peak 1. Non-transfused renal patients showed activity in peak 1 and peak 4 and in transfused renal patients the lymphocyte inhibitory activity in both peak 1 and peak 4 rose significantly ($P<0{\cdot}01$) when tested with both allogeneic and autologous lymphocytes compared with non-transfused renal patients. In both transfused groups inhibitory activity was noted in peak 2 against allogeneic lymphocytes only. Haemophiliacs showed significantly greater peak 1 activity than did normal subjects ($P<0{\cdot}01$), though, unlike renal patients, no peak 4 activity was measurable.

Thus, much of the inhibitory activity appeared to lie in peak 1, the macroglobulin peak, especially against autologous lymphocytes. In recent years, there has been much interest in the immunoregulatory activity of plasma macroglobulins, particularly alpha-2 macroglobulin (Cooperband et al., 1976; Davis et al., 1978; Stein-Streilein and Hart, 1978), and, for this reason, the effect on the inhibitory activity of removing alpha-2 macroglobulin from plasma was studied using immuno-adsorbent chromatography.

Immuno-adsorbent chromatography for alpha-2 macroglobulin

Alpha-2 macroglobulin (α2M) was removed from plasma by immuno-adsorbent chromatography utilizing rabbit anti-human α2M conjugated sepharose 4B (McEntire, 1978). Two sepharose columns were set up in 5 ml blood syringes; in one, rabbit anti-human α2M was conjugated to the sepharose and in the other (the control column) normal rabbit serum was conjugated. One millilitre of fresh plasma was divided into $2 \times 0{\cdot}5$ ml samples and each was applied to, incubated with and then washed through either the anti-α2M column or the control column. The concentration of α2M was determined before and after each column run using rocket electrophoresis (Axelsen et al., 1973). Similarly, the lymphocyte inhibitory activity of each plasma was assessed before and after each column run against allogeneic and autologous lymphocytes, the post-column values being corrected back to the original volume and dilutions of plasma.

^{125}I-labelled IgG was eluted from both columns to check that non-specific binding of protein to the conjugated sepharose was not occurring. The recovery rate of IgG from both columns was greater than 95 per cent.

Plasma samples were then passed through the columns. In the elutions from the anti-α2M column, α2M could not be detected using rocket electrophoresis, whereas there was a greater than 90 per cent recovery from the control column.

The inhibitory activity of plasma on allogeneic and autologous lymphocytes before and after each column run is shown in *Table III*. Elutions from the control column showed little change in inhibitory activity compared with pre-column values against either allogeneic or autologous lymphocytes. However, there was a very significant reduction in the inhibitory activity of plasma eluted from the anti-α2M column on allogeneic and autologous lymphocyte responses to PPD.

Thus the removal of α2M from plasma was associated with a large fall in the inhibitory activity of plasma. The inhibitory activity of plasma was not related to the concentration of α2M (*Table IV*) determined by rocket electrophoresis. Only in the haemophiliac patients was a slight rise in the α2M concentration noted.

Throughout this investigation, lymphocytotoxicity of test plasma samples on allogeneic cells was not detected.

Evaluation of alpha-2 macroglobulin in the rat

Attempts to prolong allografts in rodents using human α2M have met with mixed success in the past. Kamrin (1959) and Mowbray (1963a) were successful in prolonging graft survival, whereas Davis and Boxer (1965) failed.

To evaluate α2M, the heterotopic cardiac allograft model in inbred rats (described by Ono and Lindsey, 1969) was used (heart donor PVG/C—serotype AgB5; recipient WAG—serotype AgB2). α2M, prepared from Cohn fraction IV of pooled normal human plasma (Ford et al., 1973), was given to the recipient in two 25 mg i.v. doses, the first 24 h prior to transplantation and the second 24 h after transplantation. The results are shown in *Table V*. Following macroglobulin therapy, a mean graft survival time of 10·6 days was achieved compared with 7·3 days in untreated rats and 7·2 days in rats receiving 25 mg human albumin i.v. 24 h before and 24 h after transplantation. This prolongation of graft survival was highly significant. In the control groups no rat heart graft survived beyond 8 days compared with a minimum survival of 9 days in the macroglobulin-treated rats.

Discussion

Kamrin (1959) was the first to draw attention to the immunosuppressive properties of α2M by demonstrating prolonged skin allograft survival in rats following its administration. Mowbray (1963a) successfully repeated this work, and suggested (Mowbray, 1963b) that it was effective in the inductive phase of antibody production. As previously noted, not all workers were successful (Davis and Boxer, 1965). However, following work by Mannick and Schmid (1967), who prolonged skin allograft survival in mice following α2M therapy, the immunosuppressive properties of naturally occurring plasma proteins, in particular the α-globulins and glycoproteins including α2M, have been described in a wide variety of conditions. Some of these are pregnancy (Gaugas, 1974), cancer (Glasgow et al., 1974) and transplantation (Riggio et al., 1969). Cooperband et al. (1976) extensively reviewed these apparently non-antigen-related immunosuppressive factors. Some recent work has suggested that plasma glycoproteins may induce the lymphocyte hyporesponsiveness and insulin resistance which is seen in diabetics who become pregnant or develop cancer (Davis et al., 1978).

This study has shown that plasma from transfused patients showed a much greater ability to inhibit the responses of allogeneic and autologous lymphocytes to the non-specific antigen PPD. All the allogeneic lymphocytes came from persons known to respond to tuberculin. Less was known of the renal patients. It was regarded as unethical that patients who might shortly receive a transplant should be skin tested. Equally, the interpretation of skin testing in renal patients might be difficult as it is well known that uraemic patients possess a degree of cellular anergy (Roitt, 1977). However, all the patients came from the local population, the large majority of whom are sensitized to tuberculin.

When plasma was fractionated on G200 Sephadex much of the lymphocyte inhibitory activity was found in the macroglobulin region in both transfused and non-transfused patients. The inhibitory activity in the macroglobulin fraction was much greater in the transfused patients.

Removing α2M from plasma by immuno-adsorbent chromatography resulted in a very significant fall in the inhibitory activity to both allogeneic and autologous lymphocytes (*Table III*). Any residual activity was presumably due to either γ-globulin, or, in the case of renal patients, to the low molecular weight fraction, peak 4. Against autologous lymphocytes it is likely that the residual activity seen in the plasma from renal patients is due only to the low molecular weight fraction, as no γ-globulin activity was detected (*Table II*). The low molecular weight fraction has yet to be fully characterized.

Cellular anergy in uraemic patients has already been referred to. In a study to be reported shortly (Proud, 1979), the cellular anergy has been shown to be a separate factor from the lymphocyte inhibitory activity of plasma in both transfused and non-transfused renal patients.

Immunosuppressive activity of the alpha globulin is not species specific (Stein-Streilein and Hart, 1978). Thus, the demonstration of the ability of α2M to prolong cardiac allograft survival in rats is an indication of the important immunoregulatory activity it exhibits. The rise in lymphocyte inhibitory activity of plasma following transfusions related to α2M might offer an explanation for the subsequent renal allograft survival seen in these patients.

Whilst the inhibitory activity of plasma rose following transfusions, an increase in the concentration of α2M did not necessarily follow. Glasgow et al. (1974) and others have reported that an immunosuppressive low molecular weight peptide that is recoverable from α-globulins is present in greater concentration in cancer patients. Some early work in our own laboratory has suggested that a low molecular weight peptide can be recovered in greater quantity by dialysis from transfused renal and haemophiliac patients. α2M may be acting as a carrier protein for an active low molecular weight fraction which could be lymphocyte-derived.

A prospective study is being carried out to determine whether the lymphocyte inhibitory activity of plasma, as described in this paper, is of prognostic value in clinical transplantation when measured in the recipient immediately prior to receiving a renal allograft. It is too early to draw any conclusions. However, we have studied plasma obtained from a series of consecutive renal transplant recipients immediately prior to transplantation 5 years ago, and since stored at −20 °C. Whilst recognizing that the inhibitory activity of plasma falls slowly with storage, a significant correlation was found between lymphocyte inhibitory activity of plasma and graft survival. Greater lymphocyte inhibitory activity was associated with improved graft survival (Shenton, 1979).

Shumway and his colleagues (Coulson et al., 1976) suggested that naturally occurring immunosuppressive proteins could be used therapeutically. If the prospective studies confirm the findings described here, the use of alpha-2 macroglobulin in the treatment protocol of renal transplant recipients will need to be assessed.

References

BARNES B. A. (1965) Survival data of renal transplantations in patients. *Transplantation* 3, 812–821.

BØYUM A. (1968) Separation of leucocytes from blood and bone marrow. *Scand. J. Clin. Lab. Invest.* 21, Suppl. 97.

COOPERBAND S. R., NIMBERG R., SCHMID K. et al. (1976) Humoral immunosuppressive factors. *Transplant. Proc.* 8, 225–242.

COULSON A. S., ZEITMAN V. H., STINSON E. B. et al. (1976) Immunodepressive serum treatment of acute heart transplant rejection. *Br. Med. J.* 1, 749–750.

DAVIS J. C., FINN R., HIPKIN L. J. et al. (1978) Do plasma glycoproteins induce lymphocyte hyporesponsiveness and insulin resistance? *Lancet* 2, 1343–1345.

DAVIS W. C. and BOXER L. A. (1965) Effects of alpha 2-glycoprotein on the immune response. *Transplantation* 3, 673–676.

DEWAR P. J. and MURRAY S. (1976) Lymphocytotoxic antibody detection and crossmatching for renal transplantation. *Transplantation* 21, 387–390.

FEHRMAN I., LUNDGREN G., MAGNUSSON G. et al. (1978) Pretransplant dialysis and blood transfusion. Correlation with cadaveric kidney graft survival. Given at the Seventh International Congress of the Transplantation Society, Rome.

FORD W. H., CASPARY E. A. and SHENTON B. K. (1973) Purification and properties of a lymphocyte inhibition factor from human serum. *Clin. Exp. Immunol.* 15, 169–179.

GAUGAS J. M. (1974) Glycoproteins in pregnancy serum which interact with conconavalin A and may suppress lymphocyte transformation. *Transplantation* 18, 538–541.

GLASGOW A. H., NIMBERG R. B., MENZOIAN J. O. et al. (1974) Association of anergy with an immunosuppressive peptide fraction in the serum of patients with cancer. *N. Engl. J. Med.* 291, 1263–1267.

KAMRIN B. B. (1959) Successful skin homografts in mature non-littermate rats treated with fractions containing α-globulins. *Proc. Soc. Exp. Biol. Med.* 100, 58–61.

MCENTIRE J. E. (1978) Purification of alpha-2 macroglobulin by immuno-adsorbent chromatography. *J. Immunol. Methods* 24, 39–45.

MANNICK J. A. and SCHMID K. (1967) Prolongation of allograft survival by an alpha globulin isolated from normal blood. *Transplantation* 3, 1231–1245.

MOWBRAY J. F. (1963a) Effect of large doses of α_2 glycoprotein fraction on the survival of rat skin homografts. *Transplantation* 1, 15–20.

MOWBRAY J. F. (1963b) Ability of large doses of an alpha 2 plasma protein fraction to inhibit antibody production. *Immunology* 6, 217–225.

MURRAY S., DEWAR P. J., ULDALL P. R. et al. (1974) Some important factors in cadaver-donor kidney transplantation. *Tissue Antigens* 4, 548–557.

ONO K. and LINDSEY E. S. (1969) Improved technique of heart transplantation in rats. *J. Thorac. Cardiovasc. Surg.* 57, 225–229.

OPELZ G., SENGAR D. P. S., MICKEY P. R. et al. (1973) Effect of blood transfusions on subsequent kidney transplants. *Transplant. Proc.* 5, 253–259.

PERKINS H. A. (1977) HLA antigens and blood transfusion: effect on renal transplants. *Transplant Proc.* 9, Suppl. 1, pp. 229–232.

PERSIJN G. G., VAN HOOFF J. P., KALFF M. W. et al. (1977) Effect of blood transfusions and HLA matching on renal transplantation in the Netherlands. *Transplant Proc.* 9, 503–505.

PROUD G. (1979) Hunterian Lecture, June 1979. (Text in preparation.)

RIGGIO R. R., SCHWARTZ G. H., BULL F. G. et al. (1969) Alpha-2 globulins in renal graft rejection. *Transplantation* 8, 689–694.

ROITT I. M. (1977) *Essential Immunology*, 3rd ed. Oxford, Blackwell Scientific Publications, p. 247.

SHENTON B. K. (1979) Unpublished data.

SHENTON B. K., PROUD G., SMITH B. M. et al. (1978) Blood transfusion and renal transplantation. *Lancet* 1, 824.

STEIN-STREILEIN J. and HART D. A. (1978) Role of alpha globulins in non-specific regulation of the immune response: possible mechanisms for external and internal signals. *Fed. Proc.* 37, 2042–2044.

ULDALL P. R., DEWAR P. J., MORLEY A. R. et al. (1977) Factors affecting the outcome of renal transplantation in Newcastle upon Tyne. *Lancet* 2, 316–319.

WEEKE B. (1973) Rocket immunoelectrophoresis. In: AXELSEN N. H., KRØLL J. and WEEKE B. (ed.) *A Manual of Quantitative Immunoelectrophoresis: Method and Applications.* Oslo, Universitets Forlaget.

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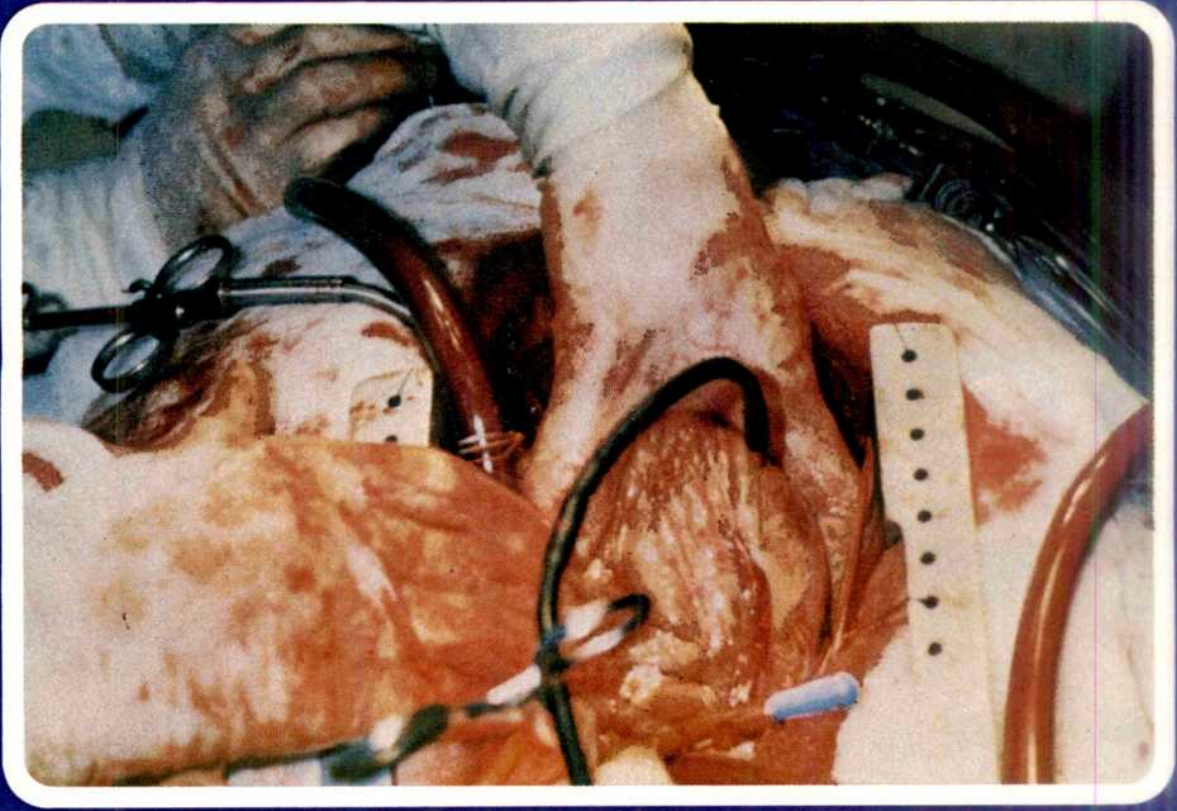

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1. Brit. med. J. (1978), **1**, 1603
2. Thorax (1978), 33, **1**, 130
3. Brit. med. J. (1978), **2**, 536
4. Brit. med. J. (1970), **4**, 455
5. Zbl. Bakt. Hyg., I. Abt. Orig. A. (1976), **236**, 235.

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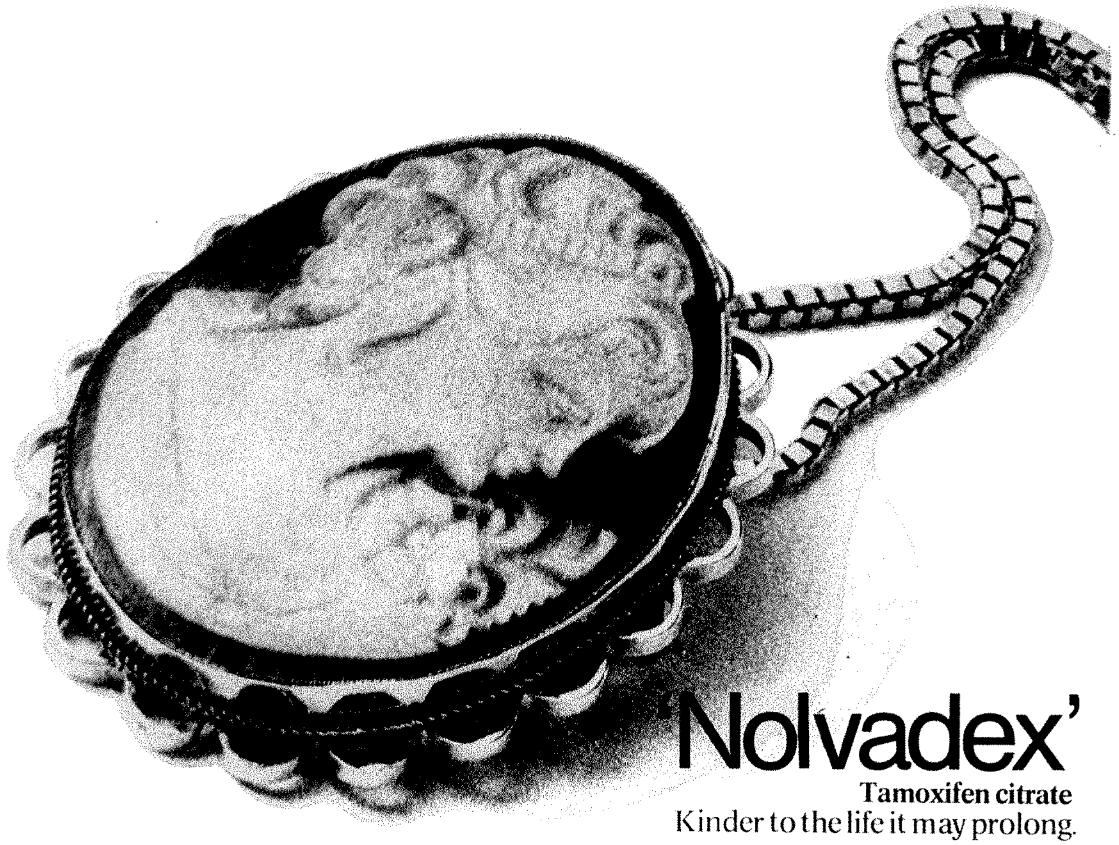
1. *Cancer Treatment Reports* (1976), **60**, 1431.
2. *British Journal of Cancer* (1971), **25**, 270



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Breast cancer and prostaglandins: a new approach to treatment

D. J. LEAPER, B. T. FRENCH AND A. BENNETT*

SUMMARY

The effect of the non-steroidal inhibitor of prostaglandin synthesis, flurbiprofen, has been studied on a transplanted mouse mammary tumour of spontaneous origin. Daily administration of 2·5 mg/kg flurbiprofen significantly reduced the growth of this NC adenocarcinoma transplanted subcutaneously into the right flank of WHT/Ht mice. Histological examination showed that primary tumours excised at 3 weeks from treated mice tended to have a more prominent lymphocytic infiltration. There was a non-significant tendency for mice treated with flurbiprofen alone to survive longer after tumour excision and to develop less local metastases, although scar recurrences seemed unaffected. The effect of adjuvant chemotherapy and local radiotherapy on local metastases and survival time tended to be greater when flurbiprofen was also given. This work supports and extends the basis for prospective clinical trials to evaluate the role of prostaglandins in human cancer and the value of prostaglandin synthesis inhibitors in cancer therapy.

CANCER of the breast is the commonest neoplasm in women and carries a poor prognosis (World Health Statistics Report, Logan, 1975). Survival figures for so-called 'early' breast cancer have changed little between the report by Halsted in 1907 and a recent trial (Report on an International Multicentre Trial supported by the Cancer Research Campaign, 1976).

The prostaglandins and related substances can be formed throughout the body, and they contribute to various physiological and pathological processes, including several aspects of malignant disease. Animal (Humes and Strausser, 1974; Tashjian et al., 1974; Galasko and Bennett, 1976) and human (Bennett, Charlier et al., 1977; Bennett, del Tacca et al., 1977) tumours can synthesize relatively large amounts of prostaglandin-like material. The most aggressive human malignant breast tumours, as shown by spread to bone or by histological examination, yield the largest amounts of postglandin-like material during tumour homogenization (Bennett, Charlier et al., 1977). Furthermore, those patients whose tumours produce most prostaglandins die soonest of their disease (Bennett et al., 1979).

Experiments presented previously and in this study used a transplantable mouse tumour of low immunogenicity which originally arose spontaneously in mouse mammary gland (Hewitt et al., 1976). The tumour can synthesize large amounts of prostaglandin E_2-like material, as indicated by thin-layer chromatography and bioassay (Bennett et al., 1978). In previous experiments, flurbiprofen, a non-steroidal anti-inflammatory drug which inhibits prostaglandin synthesis, reduced primary tumour growth, increased survival time following tumour resection—provided that treatment was started just before tumour transplantation—and substantially reduced the size of established tumours when used in combination with radiotherapy with or without chemotherapy (Bennett et al., 1978, 1979; Leaper, Bennett, Charlier et al., 1978; Leaper, Bennett, Houghton et al., 1978). In this study we report the effects of a lower dose of flurbiprofen on primary tumour growth, response to conventional anti-cancer treatment and formation of local recurrences, and examine a possible mode of action of flurbiprofen.

Table I: HISTOLOGICAL ASSESSMENT OF PRIMARY TUMOURS

	Score 7		Score 8		Score 9	
	F	C	F	C	F	C
Tumour grade	3	3	8	6	20	21
	Slight		Intermediate		Prominent	
	F	C	F	C	F	C
Lymphocytic infiltration	21	27	5	3	5	0
Tumour necrosis	5	4	8	9	18	17
Fibroblastic reaction	27	27	4	3	0	0

F, Flurbiprofen-treated group; C, control (syrup) group.
Three tumours omitted because of inadequate histological preparation.

Materials and methods

NC carcinoma was injected subcutaneously into 112 WHT/Ht mice which were treated orally with drugs as described in our previously cited work. Half received vehicle alone (raspberry syrup BP) and half were given 2·5 mg/kg flurbiprofen daily. The primary tumours were excised with a narrow rim of tissue at 3 weeks under ether anaesthesia and weighed. Thirty-two tumours from each group were fixed in formalin and prepared for routine paraffin histological slides and stained with haematoxylin, eosin and van Gieson's stains. They were then assessed blindly for tumour grade (based on a scoring system described by Bloom and Richardson, 1957), lymphocytic infiltration, tumour necrosis and fibroblastic reaction (as slight, intermediate or prominent).

Groups of mice (7 male, 7 female originally, but there were 4 anaesthetic deaths and 3 subsequent early deaths with no signs of tumour) were then given the following treatment: local radiotherapy (500 rad on the seventh and fourteenth days after tumour excision), and/or adjuvant chemotherapy weekly for 6 weeks (0·15 mg/kg melphalan on the first to third day, and 0·2 mg/kg methotrexate on the first day of each week starting 1 week after tumour excision). The two largest diameters (L and W) of local metastases and scar recurrences, seen 1–2 weeks after tumour excision, were measured weekly and the volumes were calculated from the formula volume $= \pi W^2 L/6$. All mice were observed until they died of cancer or were humanely killed (Bennett et al., 1979).

Results

Primary tumours excised at 3 weeks were significantly smaller in the mice given flurbiprofen—0·12 g ± 0·02 (mean ± s.e.mean)—than in controls—0·22 g ± 0·02 ($P < 0{\cdot}001$, Student's t test).

The 64 tumours that were assessed histologically were all poorly differentiated, scoring between 7 and 9 (9 being the poorest grade on the scale). They showed

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Table II: PERCENTAGE INCIDENCE AND MEAN VOLUMES (cm³) OF LOCAL METASTASES AND SCAR RECURRENCES IN THE EIGHT TREATMENT GROUPS

	% incidence weeks after tumour excision														
	4			5			6			7			8		
Treatment group	*n*	L	S	*n*	L	S	*n*	L	S	*n*	L	S	*n*	L	S
Control	13	77	77	13	77	77	12	83	75	11	91	73	6	100	50
Flurbiprofen	11	45	73	11	45	73	10	40*	70	7	29**	71	6	33	67
Chemotherapy	13	62	54	13	62	62	13	62	62	12	58*	67	7	43	71
Flur-chemo	13	38**	77	13	54	77	13	62	77	12	58*	67	7	29	57
Radiotherapy	14	64	86	13	77	77	12	75	83	9	67	78	6	50	50
Flur-radio	13	46*	69	13	54	69	13	62	69	9	56*	67	6	50	83
Chemo-radio	12	50	67	11	82	64	11	91	55	11	91	64	6	83	50
Flur-chemo-radio	13	23***	100	12	42*	100	12	58	100	10	60	100	8	50	100

	Mean volumes									
	L	S	L	S	L	S	L	S	L	S
Control	4·57	0·27	5·74	0·50	6·41	0·76	8·92	1·12	7·26	1·22
Flurbiprofen	1·30	0·22	3·05	0·78	3·43	1·25	2·21**	2·25	3·91	3·80
Chemotherapy	2·30	0·58	3·43	0·88	6·23	1·25	5·55	1·85	1·69	4·93
Flur-chemo	0·94*	0·77	2·70	1·29	3·53	2·73	4·50	1·95	4·20	3·78
Radiotherapy	1·98	0·21	3·40	0·26	2·85	0·46	1·95	0·98	1·54	0·82
Flur-radio	0·57*	0·13	1·17	0·44	1·90	0·83	3·21	0·93	3·44	1·71
Chemo-radio	1·09	0·27	1·89	0·28	2·44	0·54	3·71	0·79	2·95	0·98
Flur-chemo-radio	0·17**	0·26	0·38**	0·64	0·78***	0·91	1·36**	1·00	1·41	1·74

L, Local metastases; S, scar recurrence; *n*, number of mice still alive/group.
Mean volumes are given rather than median, since although the data were not normally distributed the mean values give more information because many medians were zero.
* $P \leqslant 0{\cdot}1$; ** $P \leqslant 0{\cdot}05$; *** $P < 0{\cdot}01$ compared to controls.

Table III: PERCENTAGE INCIDENCE AND VOLUMES (cm³±s.e.mean) OF LOCAL METASTASES AND SCAR RECURRENCES IN COMBINED GROUPS

Weeks after tumour excision	Local metastases					
	Flurbiprofen			Control		
	n	% incidence	Vol.	*n*	% incidence	Vol.
4	50	38**	0·73±0·17***	52	63	2·52±0·55
5	49	49**	1·81±0·39**	50	74	3·69±0·74
6	48	56*	2·37±0·54**	48	77	4·56±0·88
7	38	53**	2·94±0·72*	43	77	5·21±1·18
8	27	41**	3·13±1·11	25	68	3·29±0·86
	Scar recurrences					
4	50	80	0·35±0·14	52	71	0·33±0·10
5	49	80	0·79±0·24*	50	70	0·49±0·14
6	48	79	1·45±0·36*	48	69	0·76±0·17
7	38	76	1·52±0·31	43	70	1·21±0·22
8	27	78	2·72±0·67	25	56	2·11±0·78

n= Number of mice still alive/group.
* $P < 0{\cdot}1$; ** $P < 0{\cdot}05$; *** $P < 0{\cdot}01$ compared to controls.

Table IV: SURVIVAL TIME IN THE EIGHT TREATMENT GROUPS

	Survival time (d)
Control	73 (67–90)
Flurbiprofen	77 (65–85)
Chemotherapy	76 (70–90)
Flur-chemo	78 (72–92)
Radiotherapy	73 (69–81)
Flur-radio	72 (68–85)
Chemo-radio	77 (71–86)
Flur-chemo-radio	82 (70–94)

Values for survival time are medians and semi-quartile ranges.

no significant differences between test and controls except that lymphocytic infiltration tended to be greater in the tumours from flurbiprofen-treated mice (Fisher's exact test, $0{\cdot}1 > P > 0{\cdot}05$) (*Table I*). Scar recurrences and local metastases, defined as satellite growths of tumour connected by invaded lymphatic vessels to a primary tumour or its scar, were easily measurable 4 weeks after primary tumour excision. The most striking findings were a consistently lower volume and an initial lower incidence of local metastases in mice treated with flurbiprofen plus radiotherapy plus chemotherapy (*Table II*). Compared with controls, no treatment had a significant effect on scar recurrences, but their incidence was higher in mice given all three treatments compared with radiotherapy plus chemotherapy ($P < 0{\cdot}05$ weeks 4–6, Mann–Whitney U test). When flurbiprofen groups are combined regardless of other treatment, these show a significantly lower incidence and volume of local metastases compared with controls (*Table III*), but scar recurrences tended to be larger.

Survival times after tumour excision tended to be longer in mice given combined radiotherapy and chemotherapy than in controls, and to be further increased with the addition of flurbiprofen, but these trends were not statistically significant ($P > 0{\cdot}1$, *Table IV*). Nine weeks after tumour excision less than one-third of the mice remained alive.

Discussion

Flurbiprofen 5 mg/kg daily given to WHT/Ht mice inhibits prostaglandin synthesis in NC primary tumours (Bennett et al., 1978, 1979; Leaper, Bennett, Charlier et al., 1978; Leaper, Bennett, Houghton et al., 1978). Indomethacin inhibits prostaglandin synthesis in other animal tumours (Tashjian et al., 1974; Galasko and Bennett, 1976), and also reduces primary tumour growth (Tashjian et al., 1973; Plescia et al., 1975). The current study has shown a halving of primary tumour weights at 3 weeks with flurbiprofen at half the previous dosage (Bennett et al., 1978, 1979; Leaper, Bennett, Houghton et al., 1978), but it did not cure the mice of cancer. Humes et al. (1974) found that indomethacin delayed the appearance of murine tumours induced by Moloney sarcoma virus, so that indomethacin in these animal tumours may be cytostatic but not cytotoxic. However, indomethacin frequently prevented the appearance of transplanted methylcholanthrene-induced tumours in the experiments of Lynch et al. (1978).

Low dose chemotherapy and radiotherapy were used in the present experiments to mimic their clinical adjunctive effect to surgery, at doses similar to those used in a current trial in patients with breast cancer (Murray et al., 1978). The dose of radiotherapy was also small, being towards the lower end of the range of accepted 'normal' dosage given prophylactically after mastectomy (Report on an International Multicentre Trial, 1976). In previous experiments 5 mg/kg flurbiprofen daily enhanced the effect of this low dose cancer therapy on the growth of NC primary tumours (Bennett et al., 1978, 1979; Leaper, Bennett, Houghton et al., 1978). Half this dose in the present study enhanced the effect of radiotherapy plus chemotherapy on the incidence and volume of local metastases, but had little effect on scar recurrence. Unfortunately, no studies were done to determine the ability of the lower dose of flurbiprofen to inhibit prostaglandin synthesis to an adequate extent or for an adequate period. This may also explain why, unlike our previous results, the prolongation of survival with flurbiprofen was not statistically significant.

In a previous paper (Bennett et al., 1979) we reported no effect of 5 mg/kg flurbiprofen on local metastases. However, in that work the metastases were measured at death and not at precise times after tumour excision. Since the flurbiprofen-treated mice lived longer, the local metastases had longer to develop.

All the NC tumours were poorly differentiated according to the Bloom and Richardson scoring system. Although the reduction of tumour growth was not clearly explained by the histological findings, flurbiprofen may have enhanced an immunological response. Alternatively, more lymphocytes may have been present because greater tumour necrosis was occurring. Bloom et al. (1970), in a large study of human breast cancer, showed that 10 per cent had an intense lymphocytic infiltration, and over a 20-year period women with tumours in this category fared better. Other evidence in mice (Plescia et al., 1975) indicates that indomethacin may reduce tumour growth by removing a prostaglandin-induced inhibition of the immune system, but this may be only part of the explanation (Humes et al., 1974) or possibly unrelated (Lynch et al., 1978).

Powles et al. (1978) have shown that flurbiprofen or indomethacin can restore the efficacy of chlorambucil in rats with tumours made resistant to the drug, and Berstock et al. (1979) have found that flurbiprofen increases the survival time of mice given chemotherapy following resection of their primary tumours. The human data cited in the introduction, and the evidence from these animal experiments, emphasize the potential value of studying prostaglandins in human tumours, and of evaluating by prospective trials the place in anti-cancer therapy of drugs which inhibit prostaglandin synthesis.

References

BENNETT A., CHARLIER E. M., MCDONALD A. M. et al. (1977) Prostaglandins and breast cancer. *Lancet* **2**, 624–626.

BENNETT A., HOUGHTON J., LEAPER D. J. et al. (1978) Tumour growth and response to treatment: beneficial effect of the prostaglandin synthesis inhibitor flurbiprofen. *Br. J. Pharmacol.* **63**, 356P–357P.

BENNETT A., HOUGHTON J., LEAPER D. J. et al. (1979) Cancer growth, response to treatment and survival time in mice: beneficial effect of the prostaglandin synthesis inhibitor flurbiprofen. *Prostaglandins* **17**, 179–191.

BENNETT A., DEL TACCA M., STAMFORD I. F. et al. (1977) Prostaglandins extracted from tumours of human large bowel. *Br. J. Cancer* **35**, 881–884.

BERSTOCK D. A., HOUGHTON J. and BENNETT A. (1979) Improved anti-cancer effect by combining cytotoxic drugs with an inhibitor of prostaglandin synthesis. *Cancer Treatment Rev.* (In the press.)

BLOOM H. J. and RICHARDSON W. W. (1957) Histological grading and prognosis in breast cancer: a study of 1409 cases of which 359 have been followed for 15 years. *Br. J. Cancer* **11**, 359–377.

BLOOM H. J., RICHARDSON W. W. and FIELD J. R. (1970) Host resistance and survival in carcinoma of the breast: a study of 104 cases of medullary carcinoma in a series of 1411 cases of breast cancer followed for 20 years. *Br. Med. J.* **3**, 181–188.

GALASKO C. S. B. and BENNETT A. (1976) Relationship of bone destruction in skeletal metastases to osteoclast activation and prostaglandins. *Nature* **263**, 508–510.

HALSTED W. S. (1907) The results of radical operations for the cure of cancer of the breast. *Trans. Am. Surg. Assoc.* **25**, 61–79.

HEWITT H. B., BLAKE E. R. and WALDER A. S. (1976) A critique of the evidence for active host defence against cancer, based on personal studies of 27 murine tumours of spontaneous origin. *Br. J. Cancer* **33**, 241–259.

HUMES J. L., CUPO J. J. and STRAUSSER H. R. (1974) Effects of indomethacin on Moloney sarcoma virus-induced tumours. *Prostaglandins* **6**, 463–473.

HUMES J. L. and STRAUSSER H. R. (1974) Prostaglandins and cyclic nucleotides in Maloney sarcoma tumours. *Prostaglandins* 5, 183–196.

LEAPER D. J., BENNETT A., CHARLIER E. M. et al. (1978) The enhancement of radiotherapy and chemotherapy on a murine tumour using the prostaglandin synthetase inhibitor flurbiprofen. *Br. J. Surg.* **65**, 369.

LEAPER D. J., BENNETT A., HOUGHTON J. et al. (1978) Tumour growth and survival time: effect of a prostaglandin synthetase inhibitor. *Clin. Oncol.* **4**, 388–389.

LOGAN W. P. D. (1975) Cancer of the female breast. International Mortality Trends. *World Health Statistics Report* **28**, 232–251.

LYNCH N. R., CASTES M., ASTOIN M. et al. (1978) Mechanism of inhibition of tumour growth by aspirin and indomethacin. *Br. J. Cancer* **38**, 503–512.

MURRAY J. G., MACINTYRE J., LEIBERMAN D. P. et al. (1978) Toxicity of oral adjuvant chemotherapy in breast cancer. *Br. Med. J.* **1**, 408–409.

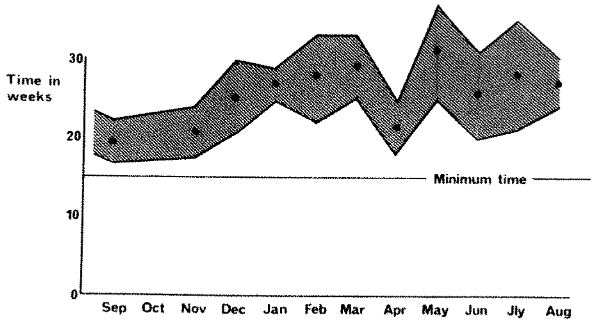
PLESCIA O. J., SMITH A. H. and GRINWICH K. (1975) Subversion of immune system by tumor cells and role of prostaglandins. *Proc. Natl Acad. Sci.* **72**, 1848–1851.

POWLES T. J., ALEXANDER P. and MILLAR J. L. (1978) Enhancement of anti-cancer activity of cytotoxic chemotherapy with production of normal tissues by inhibition of prostaglandin synthesis. *Biochem. Pharmacol.* **27**, 1389–1392.

REPORT ON AN INTERNATIONAL MULTICENTRE TRIAL SUPPORTED BY THE CANCER RESEARCH CAMPAIGN (1976) Management of early cancer of the breast. *Br. Med. J.* **1**, 1035–1038.

TASHJIAN A. H., VOELKEL E. F., GOLDHABER P. et al. (1973) Successful treatment of hypercalcemia by indomethacin in mice bearing a prostaglandin-producing tumor. *Prostaglandins* **3**, 515–524.

TASHJIAN A. H., VOELKEL E. F., GOLDHABER P. et al. (1974) Prostaglandins, calcium metabolism and cancer. *Fed. Proc.* **33**, 81–86.



Time from acceptance to publication of articles in *The British Journal of Surgery* (mean ± 1 s.d.).

Br. J. Surg. Vol. 66 (1979) 687–690

Radionuclide venography for the demonstration of the proximal deep venous system

P. G. BENTLEY AND V. V. KAKKAR*

SUMMARY

The majority of pulmonary emboli originate in the deep veins of the lower limb. Fatal emboli usually arise from thrombi that have extended into the femoral or iliac veins or lower inferior vena cava. It is often impossible to demonstrate this area, the proximal venous segment, using conventional ascending venography when there is deep venous occlusion.

The alternative methods available—retrograde, pertrochanteric and transfemoral venography—are invasive. Radionuclide venography (RNV) has been developed as a less invasive alternative. It has been found to be accurate in the proximal deep venous system when compared with conventional ascending venography, and in the presence of proximal occlusion it gives images unobtainable by other means. The radiation dose is extremely low and a perfusion lung scan is obtained without further injection of isotope. RNV appears to be the best method for monitoring the progress of thrombolytic therapy for major venous occlusion.

THE proximal venous segment includes the upper femoral, external and common iliac veins and the lower inferior vena cava. Most fatal pulmonary emboli arise from thromboses that have extended into this area from distal veins. In the presence of occlusion it is usually impossible to demonstrate the upper extent of thrombus using conventional ascending X-ray contrast venography. Alternative diagnostic procedures include retrograde, pertrochanteric and transfemoral venography, all of which are invasive and at times misleading. There is therefore a need for a simple, less invasive demonstration of the proximal venous segment, not only for the initial diagnosis but also to monitor subsequent therapy. To this end radionuclide venography (RNV) has been assessed by direct comparison with X-ray contrast venography.

Patients and methods

One hundred patients referred for venography and lung scintigraphy were studied. They included patients with acute symptoms or signs of thromboembolism or a positive fibrinogen uptake test, others undergoing assessment before varicose vein surgery and patients on treatment with anticoagulants or thrombolytic therapy. Radionuclide venography (RNV) and ascending X-ray contrast venography (XRV) were performed on the same day.

Ascending X-ray contrast venography was performed using the technique of Kakkar (1972) and radionuclide venography by the following method. The patients were examined supine on a mobile horizontal imaging table. Two 2·5-cm diameter pneumatic cuffs were applied to each leg, one just above the ankle and the other just above the knee, and connected to a bellows and pressure gauge. A cobalt-60 spot marker was placed in the midline between the legs at the level of the upper border of the patella, another just below the symphysis pubis and a third at the umbilicus. Imaging was carried out using a gamma camera (Searle Pho-Gamma III) fitted with a diverging collimator. It was found helpful to have a persistence oscilloscope linked to the camera to provide a continuous visual display of progress of the radionuclide. The pneumatic cuffs were inflated to 100–150 mmHg and a 21- or 23-gauge butterfly needle was inserted into a dorsal foot vein on each side. A three-way stopcock was connected to permit injection of radionuclide followed by a saline flush. The system was tested with saline at the beginning of each examination. The patient was then positioned for imaging of the calves, with the cobalt-60 marker between the patellas at the top of the field of view.

One mCi of $^{99}\text{Tc}^{m}$-macroaggregated albumin (MAA) was injected into each foot, followed by approximately 20 ml of saline flush. Imaging commenced and the passage of the radionuclide into the deep veins of the calf was followed on the persistence oscilloscope and recorded on Polaroid film. If necessary, each calf was gently compressed once to fill the popliteal vein. If poor calf filling was observed, additional saline was injected. Imaging was complete when 50 000 counts had accumulated. With the cuffs still inflated, the table was moved to position the patient's thighs in the field of the camera so that both cobalt-60 spot markers were in view at opposite ends of the field. Images were obtained of the femoral veins after a further injection into each foot of 1 mCi MAA. Then the patient was positioned with the camera over the pelvis and lower abdomen. The cuffs were released and, with a further 10 ml of saline flush and active ankle exercising, images of the iliac veins and inferior vena cava were obtained. Exercise continued until thirty dorsiflexions of the ankles had been performed. At this stage a persistence film of the calf region was obtained followed by similar films of the thighs and pelvis. Finally, a standard perfusion lung scan was obtained without further injection of isotope. The time taken for RNV was 15 min with an additional 15 min if a lung scan was required also. Results were available immediately on Polaroid film.

An immediate assessment of each test was made and recorded in the patient's case folder. Subsequently all films were reviewed in the absence of clinical details. A positive XRV was defined as a filling defect, present on at least two films, or an area of non-filling with collateral circulation.

A positive RNV was defined as an area of decreased radioactivity (filling defect) with or without collateral circulation; stasis of radioactivity below an obstruction or persistence of radioactivity after exercise (*Fig.* 1).

Table I: CORRELATION BETWEEN RNV AND XRV

		Overall		Calf		Thigh		Pelvis	
		XRV							
		+	–	+	–	+	–	+	–
RNV	+	68	32	59	32	18	2	17	0
	–	25	75	30	79	6	174	0	183

Results

The results are shown in *Table I.* There was an overall correlation between RNV and XRV of 71·5 per cent with 16 per cent false positive and 12·5 per cent false negative results from RNV. In the calf, there was a correlation of 69 per cent with 16 per cent false positive and 15 per cent false negative results. In the thigh, there was a correlation of 96 per cent with 1 per cent false positive and 3 per cent false negative results. In the pelvis there was 100 per cent correlation, although XRV was often unsatisfactory above the external iliac veins.

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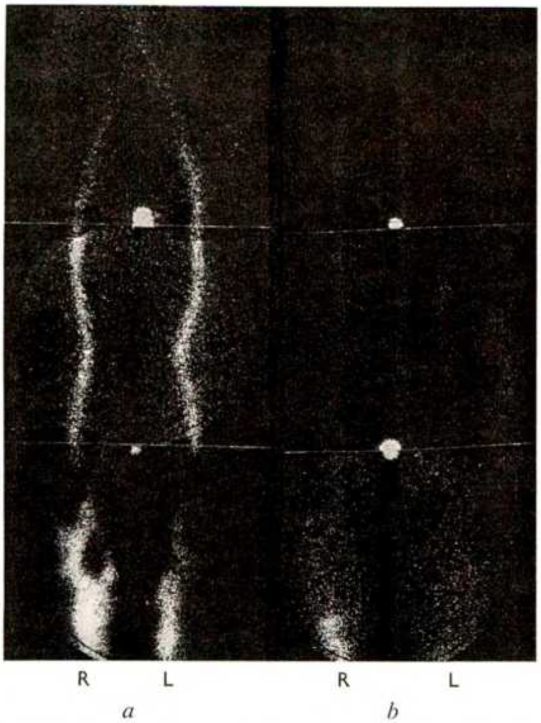

Fig. 1. Radionuclide venogram. *a*, Dynamic phase. There is a filling defect within the right calf. The remainder of the right side and the whole of the left side are normal. *b*, Static phase. There is persistence of radionuclide in the right calf distal to the filling defect.

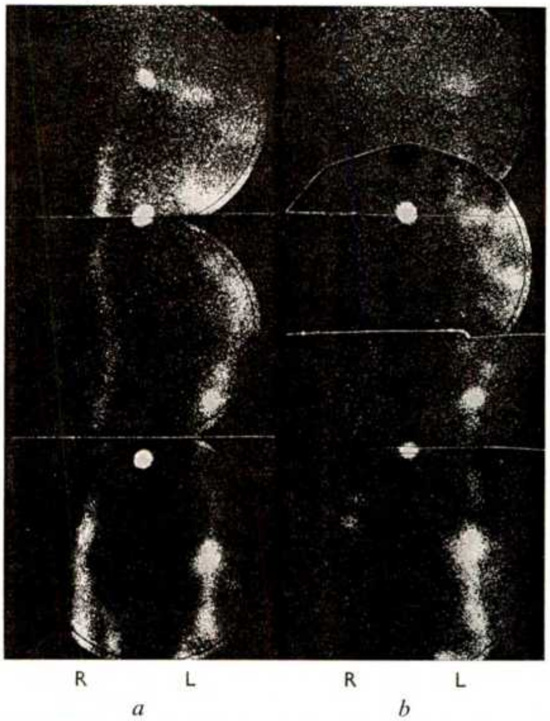

Fig. 2. Radionuclide venogram before thrombolytic therapy. *a*, Dynamic phase. The deep venous system on the left side is totally occluded up to the inferior vena cava with pooling of isotope in collateral circulation. The right side appears normal. *b*, Static phase. Radionuclide has cleared from the normal right side, but there is persistence on the left up to the level of the common iliac vein.

Minor thrombi in the calf (defined as those present in soleal veins alone or in tibial veins but less than 5 cm in length) were detected by RNV in 7 out of 13 cases (53·8 per cent) and larger calf thrombus in 20 out of 25 cases (80 per cent). In the femoral region 12 out of 13 (92 per cent) thrombi were detected. The one failure of RNV was a 5-cm non-occlusive thrombus localized to the lower femoral vein, with normal deep veins above and below it. In the proximal deep venous system RNV was positive in all 16 cases with occlusion shown on XRV. It gave a clearer outline of the iliac veins and lower vena cava than XRV, and in 11 cases showed more of the proximal venous segment than could be displayed by XRV. RNV was especially useful for monitoring the progress of thrombolytic therapy (*Figs.* 2–4).

Discussion

The use of isotopes for the demonstration of the venous system was first suggested following the chance observation of uptake of labelled macroaggregates of albumin in an area of thrombophlebitis in the arm of a patient undergoing lung scintigraphy (Webber et al., 1969). It was thought that the aggregates adhered directly to thrombus (Henkin et al., 1974) and that this effect could be reversed by heparin (Hayt et al., 1977). It is more likely, however, that persistence of radionuclide in the region of a thrombosis is due to stasis distal to the acute occlusion (Ryo et al., 1976).

The results presented in this study show that compared with XRV, RNV is progressively more accurate as imaging becomes proximal. This is emphasized in cases of proximal occlusion where RNV gives images unobtainable with conventional venography. Whereas diluted, slow moving X-ray contrast medium gives very poor resolution, no such disadvantage is seen with RNV. A slow transit time of radionuclide gives images of better definition and makes the test ideal for demonstrating the extent of occlusion where venous stasis and collateral circulation has occurred.

There is no ideal investigation for the diagnosis of acute deep vein thrombosis. The clinical features of this condition are notoriously confusing, with an accuracy of only 50 per cent when based on clinical examination alone (Lambie et al., 1970), and X-ray contrast venography remains the established diagnostic standard against which all other investigations must be compared. XRV is accurate and safe in the hands of those performing it regularly; however, it is invasive (Thomas, 1972) and there is a variable degree of discomfort for the patient together with a relatively high overall cost. Iodine sensitivity reactions may occur and the large hyperosmotic intravenous fluid load is undesirable in those patients with compromised cardiac function, although 60 per cent w/v contrast media (1480 mosmol/l) give less complications than the stronger solutions (Malins, 1978). The alternative, less invasive diagnostic procedures in common use are the fibrinogen uptake test, Doppler

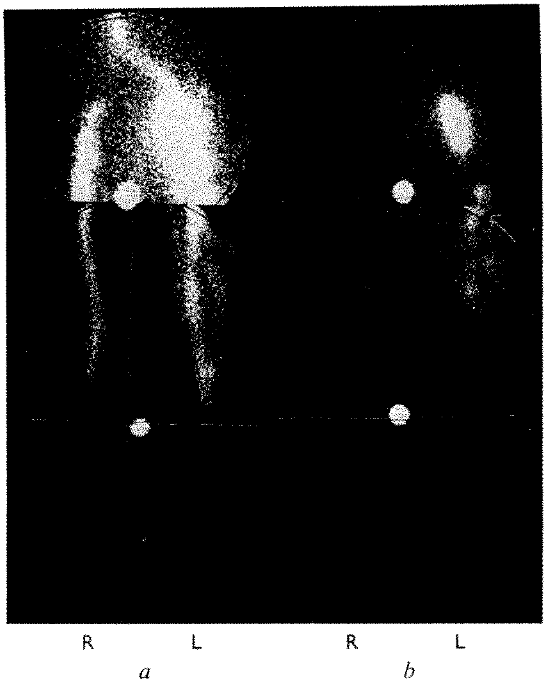

Fig. 3. Radionuclide venogram after 3 days' thrombolytic therapy. *a*, Dynamic phase. The left femoral vein is now partially open; radionuclide is trapped distal to the common iliac vein and reaches the inferior vena cava via a collateral. *b*, Static phase. Radionuclide persists on the left in the upper femoral and external iliac veins.

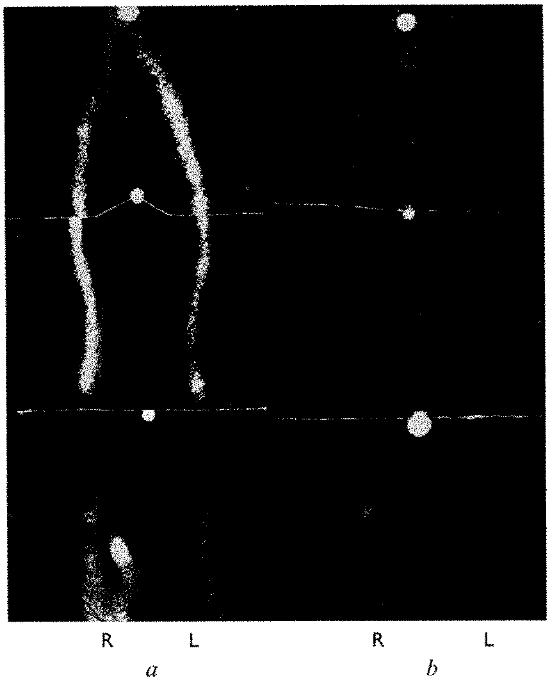

Fig. 4. Radionuclide venogram after 5 days' thrombolytic therapy. *a*, Dynamic phase. The major veins now appear normal, indicating lysis of all thrombus. *b*, Static phase. There is now no abnormal persistence of radionuclide.

ultrasound method and impedance phlebography. The former (Kakkar, 1972) is well suited to the screening of operative patients but requires at least 24 h before results are available, precluding its use as an urgent diagnostic method. In addition, it fails to give information about the deep venous system proximal to the inguinal ligaments (Browse, 1972), or to indicate the morphological extent of a thrombosis.

The Doppler ultrasound technique (Milne et al., 1971) detects only complete occlusions of the major veins and must be regarded as a crude screening test for massive thrombi. Impedance plethysmography shows promise as a useful screening test (Strandness and Sumner, 1972), but even if accurate will only serve to indicate those patients requiring venography.

RNV is certainly less invasive than conventional venography. Little expertise is necessary and apart from the insertion of a fine needle into a dorsal vein of each foot the investigation may be performed by non-medical personnel. The additional information obtained by the simple change of site of injection of isotope from an arm vein to dorsal foot veins suggests that RNV should be adopted in patients with suspected thromboembolism undergoing lung scintigraphy. The radiation dose from RNV appears to be very much less than that received during XRV. The lung radiation dose from RNV is 1·2 rad (ICRP, 1969) with an estimated fetal dose in a pregnant woman of 0·025 rad. The skin dose during XRV is 6 rad for the two abdominal films alone, with an estimated fetal dose of 1·2 rad. It would seem that with its specificity for the major veins of the pelvis, RNV should be well suited to use in suspected thromboembolism of pregnancy.

Because of inaccuracy in the calf, RNV will not yet replace XRV as the standard diagnostic procedure in suspected thromboembolism except in those centres with scanning facilities where XRV is not available. However, it is a useful addition to XRV in patients with major proximal venous occlusion where conventional venography is difficult and at times confusing and it appears to be the method of choice for monitoring the progress of thrombolytic therapy.

Acknowledgements

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References

BROWSE N. L. (1972) The ^{125}I-fibrinogen uptake test. *Arch. Surg.* **104**, 160–163.

HAYT D. B., BLATT C. J. and FREEMAN L. M. (1977) Radionuclide venography; its place as a modality for the investigation of thromboembolic phenomena. *Semin. Nucl. Med.* 7, 263–281.

HENKIN R. E., YAO J. S. T., QUINN J. L. et al. (1974) Radionuclide venography in lower extremity venous disease. *J. Nucl. Med.* **15**, 171–175.

INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION (ICRP) (1969) Publication No. 17: Protection of the patient in radionuclide investigations. Oxford, Pergamon Press, p. 78.

KAKKAR V. V. (1972) The ^{125}I-labelled fibrinogen test and phlebography in the diagnosis of deep vein thrombosis. *Milbank Mem. Fund Q.* **50**, 206–229.

LAMBIE J. M., MAHAFFY R. G. and BARBER D. C. (1970) Diagnostic accuracy in venous thrombosis. *Br. Med. J.* **2**, 142–143.

MALINS A. F. (1978) Pulmonary oedema after radiological investigation of peripheral occlusive vascular disease. *Lancet* **1**, 413–415.

MILNE R. M., GRIFFITHS J. M. J. and GUNN A. A. (1971) Postoperative deep vein thrombosis. *Lancet* **2**, 445.

RYO U. Y., COLOMBETTI L. G., POLIN S. G. et al. (1976) Radionuclide venography: significance of delayed washout; visualization of the saphenous system. *J. Nucl. Med.* **17**, 590–595.

STRANDNESS D. E. and SUMNER D. S. (1972) Ultrasonic velocity detector in the diagnosis of thrombophlebitis. *Arch. Surg.* **104**, 180–185.

THOMAS M. D. (1972) Phlebography. *Arch. Surg.* **104**, 145–159.

WEBBER M. M., BENNETT L. R., CRAGIN M. et al. (1969) Thrombophlebitis—demonstration by scintiscanning. *Radiology* **92**, 620–623.

Statistics in *The British Journal of Surgery*

It is part of the clinical scientist's stock-in-trade to use statistical methods. In many instances, and by most readers, these can be taken on trust, but in that there is a wide variety of tests and, on occasion, disagreement amongst both amateurs and professionals on the best choice, it is always wise that authors quote the method used. It is indeed journal policy to quote methods, the reason for their choice and, in the case of clinical trials, the confidence or tolerance limits of the observed results. Delay in acceptance may occur if contributors do not include these details.

Br. J. Surg. Vol. 66 (1979) 691–695

Nature of the disturbance in the body fluid compartments during and after surgical operations

W. M. ROBARTS*

SUMMARY

Haematocrit and plasma protein concentrations have been measured in patients undergoing surgical operations in order to estimate relative changes in the volumes of the extracellular and plasma compartments. That these provide valid estimates of volume changes has been shown by applying them to patients known to have lost extracellular fluid. Further confirmation that changes in haematocrit, as indices of falls in plasma volume, are valid even after surgery is provided by measurements of red cell mass, using red cells labelled with ^{99}*Tc*^{m}.

When these methods were applied to patients undergoing abdominal and non-abdominal operations, only the abdominal group showed a significant fall in plasma volume. This fall was caused not by a loss of crystalloid from the extracellular space as a whole, but by a loss of plasma; the magnitude of this loss correlated significantly with the duration of operation. These changes were also demonstrated using the radioisotope dilution indicators ^{125}*I (RISA) and* ^{131}*I (RISA).*

SINCE the 1930s there have been many studies in which fluctuations in the volumes of the body fluid compartments after major surgery have been investigated. The main interest has centred on possible changes in the extracellular volume: however, its measurement, using dilution indicators, has posed many problems.

The present study attempts to eliminate any doubts that may arise from dilution indicator techniques. It is based on the hypothesis that simultaneous measurement of haematocrit and plasma protein concentration enables a qualitative and quantitative distinction to be made between changes in the plasma compartment alone and changes in the whole extracellular space. A fall in plasma volume due to loss of plasma should cause only a rise in haematocrit, whereas a fall in plasma volume due to contraction of the whole extracellular fluid (ECF) (resulting from a loss of water and electrolytes) should cause rises both in haematocrit and in plasma protein concentration.

The hypothesis demands that in patients who are known to have lost ECF there should be parallel rises in haematocrit and plasma protein concentration and the first part of this study demonstrated this parallelism in two such groups of patients.

The second and main part of the study examined the nature of the disturbances of the body fluid compartments during the perioperative period.

Because deductions from haematocrit measurements are dependent on the constancy of the red cell mass, the third part of the study measured red cell mass changes, and compared them with direct measurements of blood loss. At the same time plasma volume changes were measured by conventional radioisotope dilution.

Patients and methods

Informed consent was obtained from the patients and the Clinical Investigations Committee of the Middlesex Hospital, and where relevant from the Isotope Advisory Panel of the DHSS.

Extracellular depletion

Simple intestinal obstruction: Fifteen patients presenting as emergencies with simple intestinal obstruction were studied. Venous blood samples were taken before and at varying intervals during resuscitation with normal saline. The haematocrit was determined in triplicate using a Hawkesley microhaematocrit centrifuge. The plasma protein concentration was measured by refractometry (Atago)—this method has been verified in the past against the biuret method (Robarts et al., 1979).

Dumping provocation tests: Ninety-three patients were given an oral glucose load (150 ml 50 per cent glucose). Peripheral blood samples were taken before ingestion and at 5, 10, 15, 20, 30, 40, 60 and 120 min afterwards. The haematocrit and plasma protein concentrations were measured as above.

Least squares regression analysis has been performed in both groups on measured plasma protein concentrations versus the value predicted from the change in haematocrit.

Estimation of plasma and extracellular volume changes

Two groups of patients were chosen.

Group 1: Intra-abdominal operations ($n = 44$)—cholecystectomy, vagotomy.

Group 2: Extra-abdominal operations ($n = 36$)—parotidectomy, thyroidectomy, mastectomy.

The anaesthetic techniques were similar in the two groups. The measured blood losses were less than 500 ml, and no blood, plasma or plasma substitutes were given to any patient. Other patient details are shown in *Table I*.

The haematocrit and plasma protein concentrations were measured immediately preoperatively, immediately postoperatively and after 4 h postoperatively.

Statistical comparisons within and between the groups have been made using Student's *t* test (paired and unpaired) for normally distributed data, and Wilkinson's rank sum test (paired and unpaired).

Table I: SUMMARY OF THE PATIENT VARIABLES IN BOTH GROUPS

	Group 1 ($n = 44$)	Group 2 ($n = 36$)
Sex	M17 F27	M14 F22
Age (yr)	51·9±13·3	49·0±14·6
Weight (kg)	66·3±13·1	68·2±10·6
Blood loss (ml)	222·0±85·6	210·3±126·9
Intravenous saline	401·6±353·9	426·7±287·8
Intravenous % theoretical ECF	2·7±2·3	2·8±1·9
Operation length (min)	85·9±31·2	109·1±26·3*

Values are mean±s.d.
* $P < 0·01$ (Wilcoxon).

Isotopic studies

Estimation of red cell mass and plasma volume changes: Two further groups of patients falling in the same categories as above were chosen. All patients were older than 25 years, and where relevant, pregnancy was excluded. Eight patients in each group had PV measurements: 10 patients in group 2 had RCM measurements. The red cell mass was measured preoperatively

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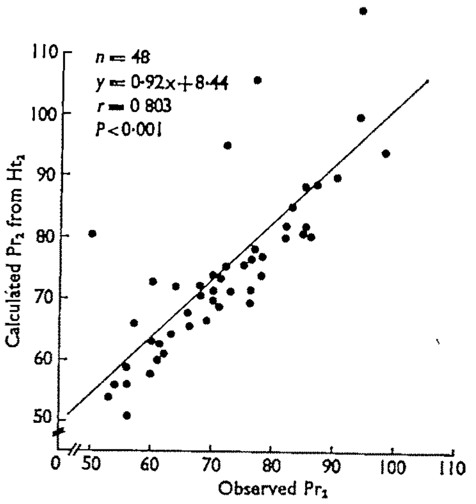

Fig. 1. Simple intestinal obstruction. Correlation between observed plasma protein concentration and that derived from the change in haematocrit (plasma protein concentrations (g/l)).

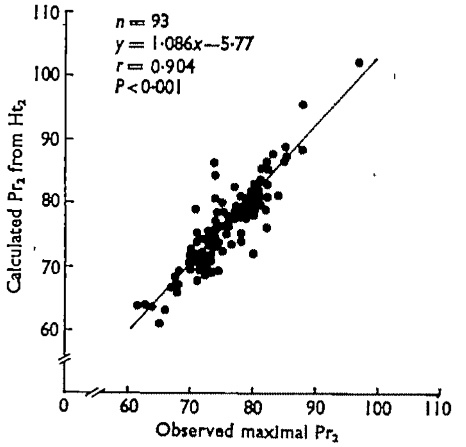

Fig. 2. Dumping provocation tests. Correlation between the observed maximal plasma protein concentration and that derived from the change in haematocrit after administration of an oral glucose load (plasma protein concentrations in g/l).

with red cells labelled with $^{99}Tc^m$ 10 μCi and postoperatively with red cells labelled with $^{99}Tc^m$ 100 μCi. The cells were labelled according to the method of Jones and Mollison (1978).

After blocking the thyroid with potassium iodide (150 mg orally 4 h before operation), the plasma volume was measured preoperatively with ^{125}I (RISA) 2 μCi and postoperatively with ^{131}I (RISA) 2 μCi. The space occupied after the operation by ^{125}I (RISA) was also measured.

Blood samples were taken through a peripheral line at 10, 15, 20 and 30 min after injection of the isotopes preoperatively. Postoperatively a sample was taken immediately before injection of the isotopes and then at 10, 15, 20 and 30 min afterwards.

The haematocrit and plasma protein concentrations were measured on each sample.

A 5-ml aliquot of saponified whole blood was counted in a J & P Counter Ratemeter MS 310 in the appropriate channels for each isotope—^{125}I and ^{131}I were counted after 48 h, by which time there were negligible counts for $^{99}Tc^m$, thus avoiding any interference from this source.

The red cell mass or plasma volume was calculated according to the formula

$$\text{RCM or PV} = \frac{\text{wt injected} \times \text{counts in 5 ml standard} \times \text{vol. standard}}{\text{wt in standard} \times \text{counts in 5 ml blood}} \times \begin{cases} \text{either } \dfrac{\text{Ht}}{100} & \text{(for RCM)} \\ \text{or } \dfrac{100-\text{Ht}}{100} & \text{(for plasma volume)} \end{cases}$$

The resulting measurements of volume were extrapolated to zero time on a semilogarithmic scale to allow for elution and decay ($^{99}Tc^m$) and extravasation (RISA).

Operative blood loss was measured by swab weighing.

All statistical comparisons were made using the Wilcoxon rank test (paired and unpaired).

Results

Extracellular depletion

Simple intestinal obstruction (*Fig.* 1): The observed plasma protein concentration in each blood sample, taken either before, during or after resuscitation, correlated very closely with the plasma protein concentration calculated from the fall in plasma volume as measured by haematocrit, i.e. crystalloid had been lost from the ECF ($r = 0{\cdot}803$, $P < 0{\cdot}001$).

Dumping provocation tests (*Fig.* 2): There was a highly significant correlation between the maximum value of plasma protein concentration and the value calculated from the haematocrit measured at the same time ($r = 0{\cdot}904$, $P < 0{\cdot}001$).

Plasma and extracellular changes after surgery

In group 1, the intra-abdominal group (*Fig.* 3), there were highly significant differences between the percentage changes in plasma volume as calculated by haematocrit and the percentage changes as calculated by plasma protein concentration. Moreover, there was a rise in haematocrit, indicating a fall in plasma volume, but no corresponding rise in plasma protein concentration. This suggests that plasma was lost from the plasma compartment, without any loss of crystalloid from the rest of the extracellular space. This loss of plasma was related to the length of operation (*Fig.* 4).

In group 2, the extra-abdominal group (*Fig.* 5), there were no significant differences between the plasma volume changes calculated from the haematocrit and those calculated from the plasma protein concentration. There was no rise in either, i.e. neither plasma nor ECF were lost, even though the length of operation in this group was significantly greater than in group 1 (*Table I*).

Isotope studies

The percentage change in red cell mass as measured by $^{99}Tc^m$-labelled red cells was compared with the change, calculated from the operative blood loss (this figure is obtained by multiplying the operative blood loss $(Ht_1 \times 0{\cdot}9)/100$ [approximate correction for whole body haematocrit] and expressing this as a percentage of the initial RCM).

There were no statistically significant differences between the changes measured by either method in either group (*Fig.* 6).

The percentage changes in plasma volume as measured before and after operation by ^{125}I (RISA) and ^{131}I (RISA) were compared in the two groups

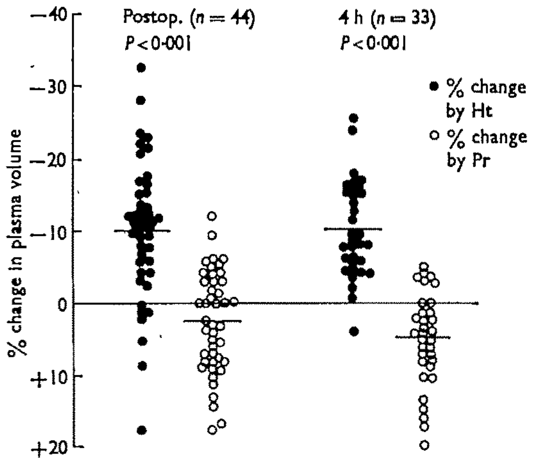

Fig. 3. Group 1. The percentage changes in plasma volume as measured by haematocrit compared with the percentage changes as measured by plasma protein concentration, immediately after operation and at 4 h.

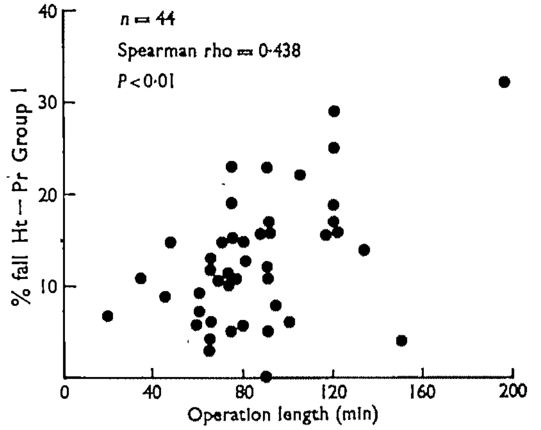

Fig. 4. The correlation between the loss of plasma, as calculated from the difference in falls in plasma volume as estimated by haematocrit and plasma protein concentration, and the length of operation.

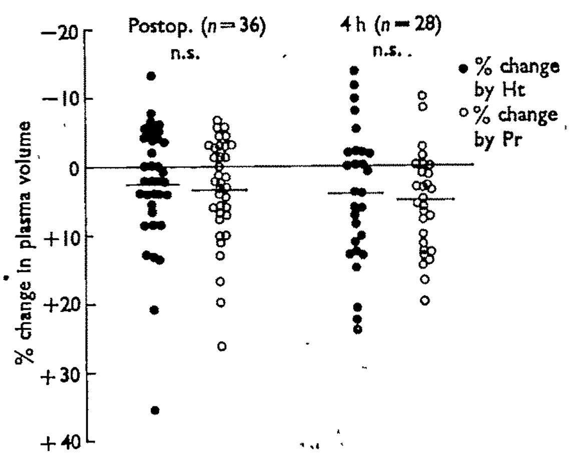

Fig. 5. Group 2. The percentage changes in plasma volume as measured by haematocrit compared with the percentage changes as measured by plasma protein concentration, immediately after operation and at 4 h.

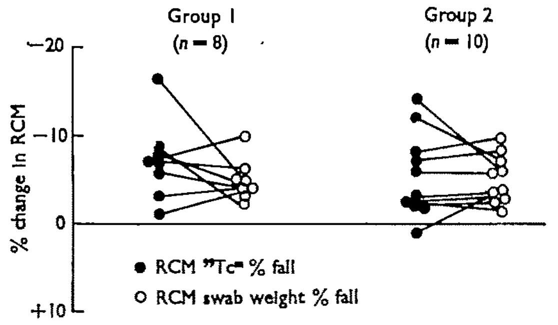

Fig. 6. The percentage changes in red cell mass in the two groups as measured by ^{99}Tc^{m}-labelled red cells compared with the percentage changes in red cell mass calculated from swab weighing of whole blood loss.

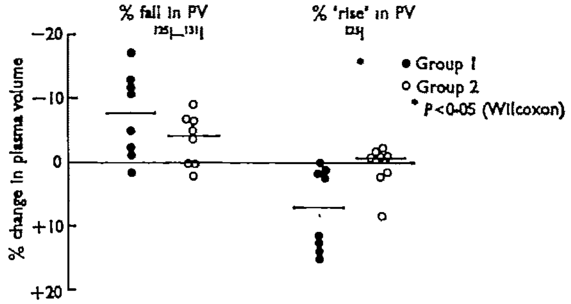

Fig. 7. The percentage changes in group 1 and group 2 in plasma volume as measured (*a*) by the difference between the volumes before and after operation as measured by ^{125}I (RISA) and ^{131}I (RISA) respectively; (*b*) by the difference in volumes occupied by the preoperative marker ^{125}I (RISA).

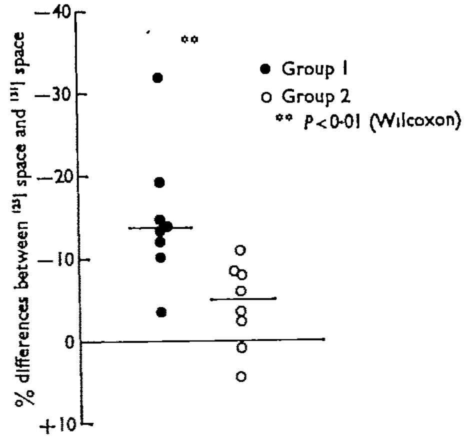

Fig. 8. A comparison of the two groups when the two volume markers (^{125}I-^{131}I and ^{125}I alone) are considered in conjunction.

after making corrections for the plasma volume fall caused by operative blood loss and for the increase in volume due to peroperative administration of intravenous crystalloid (saline) on the assumption that it is evenly distributed throughout the whole ECF (ECF calculation ♂ = 7·35 + 0·135 × BW; ♀ = 5·27 + 134 × BW [Moore et al., 1963]).

No significant difference in the fall of plasma volume could be demonstrated between the two

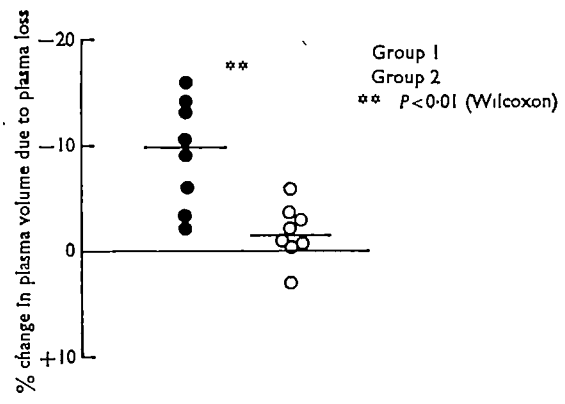

Fig. 9. Both subgroups are compared immediately postoperatively in relation to the loss of plasma as estimated by the differences between the plasma volume change as estimated by haematocrit and that by plasma protein concentrations.

groups (*Fig.* 7). A comparison of the change in volume of the space occupied by the preoperative marker ^{125}I (RISA) in the two groups did show a significant difference (*Fig.* 7). Group 1 showed the larger increase, i.e. this marker must have been diluted more in this group. Estimations of the volumes of intravenous fluids given to the group 1 patients showed significant differences (median group 1, 3·5 per cent ECF; group 2, 2·0 per cent ECF; $P<0{\cdot}05$). These findings are therefore a representation of the differences in intravenous administration.

If the contraction of plasma volume as measured by the preoperative (^{125}I) and postoperative (^{131}I) markers is considered in conjuction with the apparent rise in volume after operation as measured by the preoperative marker (^{125}I), thus nullifying the effect of the differences in intravenous administration, then there is a highly significant difference between the intra- and extra-abdominal groups (*Fig.* 8). This is also shown by the differences in the haematocrit and plasma protein concentration measurements (*Fig.* 9).

Discussion

The hypothesis that changes in plasma and extracellular volumes can be determined by measurement of haematocrit and plasma protein concentration has been discussed elsewhere (LeQuesne et al., 1960; Robarts et al., 1979).

A personal analysis of studies from the literature on patients known to have lost extracellular fluid shows close correlations between the changes in plasma volume calculated by the two methods—notably in cholera (Watten et al., 1959) and changes in posture (Eisenberg, 1963). The present studies on patients with simple intestinal obstruction, and during dumping provocation tests, confirm these findings and provide strong evidence for the validity of the hypothesis.

Previous studies have concentrated on showing apparent changes in extracellular fluid volume (ECFV) over the perioperative period. Before 1961, investigations showed an expansion of the ECFV (Stewart and Rourke, 1938; Lyon et al., 1949; De Cosse et al., 1956). In 1961 a large extracellular deficit was demonstrated postoperatively by Shires et al., and other workers produced similar results (Boba, 1966; Hoye, 1966). This led to the practice of giving large volumes of balanced salt solutions during operation. Since then these results have been criticized over the interpretation of the changing equilibration times of the marker isotope (^{35}S sulphate) used to measure ECFV (Cleland et al., 1966; Roth et al., 1969). These workers showed no difference between the ECFV before and after operation.

All these studies using dilution indicators must be criticized on the grounds that it is impossible to determine the space that any of them is entering. By measuring ratios of intrinsic components of the various compartments this criticism has been overcome, and the present studies clearly show that patients having abdominal surgery become significantly hypovolaemic following surgery and that this is brought about by a loss of plasma rather than by any overall change in the remainder of the ECF.

Where has the lost plasma gone? It has been noted before that the amount of protein which can be removed from the peritoneal cavity during abdominal surgery is greater than would be expected from the measurement of blood loss (Jarnum, 1961; Kragelund, 1971). However, these changes have not been equated with any fall in plasma volume. Hoye et al. (1972) did show large falls in plasma volume as measured by ^{125}I (RISA) but he also showed large falls in the whole extracellular volume as well, and recommended replacement with large volumes of balanced salt solutions.

The criticism that alterations in red cell mass might alter the significance of haematocrit changes could only be valid if there were a differential rise in red cell mass in the abdominal group. This did not happen, and there is no significant difference between the minimal losses measured by weighing swabs and losses calculated from the actual changes in total red cell mass. Other workers have noted similar results using ^{51}Cr-labelled red cells (Shires et al., 1961; Hoye et al., 1972).

The inability to show significant falls in plasma volume using RISA as a dilution indicator emphasizes the problems of interpretation of this technique, especially where the changes are relatively small and are masked by the effects of giving intravenous fluids. Only by combining the results of the plasma volume fall, as measured by ^{125}I (RISA) before operation and ^{131}I (RISA) after operation, with the apparent increase in the volume of ^{125}I (RISA) space due to intravenous administration, was it possible to show significant differences between the two groups. Nevertheless, a combination of these findings and the changes in haematocrit and plasma protein concentration strengthens the conclusion that there has been a significant loss of plasma in the group of patients undergoing abdominal surgery.

References

BOBA A. (1966) Support of blood volume during operation without blood transfusion. *Surg. Forum* **17**, 61.

CLELAND J., PLUTH J. R., TAUXE W. N. et al. (1966) Blood volume and body fluid compartment changes soon after closed and open intracardiac surgery. *J. Thorac. Cardiovasc. Surg.* **52**, 698–705.

DE COSSE J. J., RANDALL H. T., HABIF D. V. et al. (1956) The mechanism of hyponatraemia and hypotonicity after surgical trauma. *Surgery* **40**, 27–36.

EISENBERG S. (1963) Effect of posture and position of the venous sampling site on the haematocrit and serum protein concentration. *J. Lab. Clin. Med.* **61**, 755–760.

HOYE R. C. (1966) Blood and fluid volume deficits following extensive surgery. *Surg. Forum* **17**, 59.

HOYE R. C., BENNETT S. H., GEELHOED G. W. et al. (1972) Fluid volume and albumin kinetics occurring with major surgery. *JAMA* **222**, 1255–1261.

JARNUM S. (1961) Plasma protein exudation in the peritoneal cavity during laparotomy. *Gastroenterology* **41**, 107–118.

JONES J. and MOLLISON P. L. (1978) A simple and efficient method of labelling red cells with ^{99}Tc^{m} for determination of red cell volume. *Br. J. Haematol.* **38**, 141–148.

KRAGELUND E. (1971) Loss of fluid and blood to the peritoneal cavity during abdominal surgery. *Surgery* **69**, 285–287.

LE QUESNE L. P., HOBSLEY M. and HAND B. H. (1960) The dumping syndrome 1. Factors responsible for the symptoms. *Br. Med. J.* **1**, 141–147.

LYON R. P., STANTON J. R., FUIS E. D. et al. (1949) Body and 'available fluid' (thiocyanate) volume studies in surgical patients; normal patterns of response of blood volume, available fluid, protein chloride and haematocrit in postoperative surgical patients. *Surg. Gynecol. Obstet.* **89**, 9–19.

MOORE F. D., OLESEN K. H., MCMURRAY J. D. et al. (1963) *The Body Cell Mass and its Supporting Environment.* Philadelphia, Saunders, pp. 84–85.

ROBARTS W. M., PARKIN J. V. and HOBSLEY M. (1979) A simple clinical approach to quantifying losses from the extracellular and plasma compartments. *Ann. R. Coll. Surg. Engl.* **61**, 142–145.

ROTH E., LANE L. C. and MOLONEY J. V. (1969) Ringer's lactate solution and extracellular fluid volume in the surgical patient—a critical analysis. *Ann. Surg.* **169**, 149–164.

SHIRES T., WILLIAM J. and BROWN F. T. (1961) Acute changes in extracellular fluid associated with major surgical procedures. *Ann. Surg.* **154**, 803–810.

STEWART J. D. and ROURKE G. M. (1938) Changes in blood and intestinal fluid resulting from surgical operation and ether anaesthesia. *J. Clin. Invest.* **17**, 413–416.

WATTEN R. H., MORGAN F. H., SONGULA Y. N. et al. (1959) Water and electrolyte studies in cholera. *J. Clin. Invest.* **38**, 1879–1885.

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A lung colony clonogenic cell assay for human malignant melanoma in immune-suppressed mice and its use to determine chemosensitivity, radiosensitivity and the relationship between tumour size and response to therapy

J. MEIRION THOMAS*

SUMMARY

A lung colony assay for clonogenic cells of human tumours in immune-suppressed mice is presented. The assay was used to determine the chemosensitivity of two malignant melanomas. One tumour reproduced the spectrum of chemosensitivity associated clinically with three cytotoxic agents. The other melanoma reproduced the chemosensitivity demonstrated in the patient from whom the tumour was biopsied.

The importance of tumour size as a determinant of response to melphalan was investigated and the clonogenic cell survival in smaller tumours was found to be slightly but significantly lower than in larger tumours.

An investigation of the importance of size as a determinant of response to radiotherapy demonstrated that 0·5-mm diameter tumour nodules were significantly more sensitive to irradiation than 2-cm diameter nodules. The hypoxic fraction of the larger tumours was 65 per cent, which is higher than that reported for experimental animal tumours or a human pancreatic tumour. This could be a factor in the clinical radioresistance of malignant melanoma.

MAJOR advances in cancer chemotherapy will depend either on the development of better cytotoxic drugs or on the more efficient use of existing drugs. The development of laboratory methods for predicting the chemosensitivity of human tumours may lead to better selection of cytotoxic drugs and improvements in chemotherapy protocols.

Human tumours can be grown in laboratory animals either at immunologically privileged sites (Bradford Patterson, 1968), in nude (athymic) mice (Shimosato et al., 1976) or in artificially immune-suppressed mice (Castro, 1972). The response of tumours to cytotoxic agents is frequently assessed by monitoring volume change after treatment, but this method has been shown to be less sensitive than the assessment of clonogenic cell survival (Hermens and Barendsen, 1969). Cytotoxic agents preferentially kill proliferating cells, and because most tumour cells are non-proliferating, significant stem cell kill may have occurred with little or no change in tumour volume.

Two *in vitro* clonogenic cell assays have previously been described for human tumours (Smith et al., 1976; Courtenay and Mills, 1978), and this paper describes the first *in vivo* assay. The development of the *in vivo* lung colony assay has been made possible by a recent improvement in the method of immune suppression of CBA/lac mice (Steel et al., 1978; derived from the work of Millar, 1976). (A clonogenic cell is defined as a stem cell which on extraction from a tumour to a test environment retains the ability to produce a large family of descendants.)

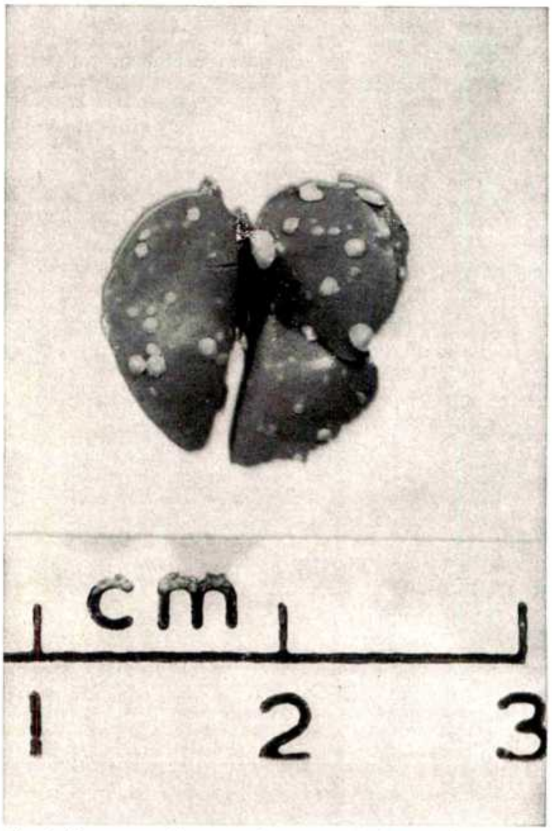

Fig. 1. Human malignant melanoma colonies on the lung surface of CBA mice.

Materials and methods

Male CBA/lac mice were immune suppressed by thymectomy and pretreatment with cytosine arabinocide (Ara-C) (200 mg/kg) 48 h before 900 rad total body irradiation.

It was observed that the i.v. injection of a single cell suspension of human malignant melanoma cells resulted in lung surface colonies (*Fig.* 1), and that there was a linear relationship between the number of cells injected and the number of lung surface colonies produced.

The lung colony assay

The assay (*Fig.* 2) was developed using two human malignant melanoma xenografts (laboratory designation HX34 and HX46). HX34 was obtained by biopsy of a metastatic cervical

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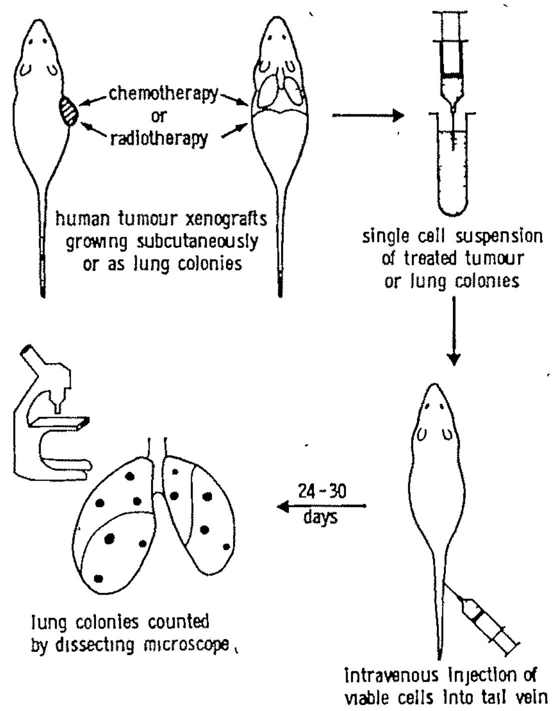

Fig. 2. The technique of lung colony assay of a treated subcutaneous tumour or lung colonies.

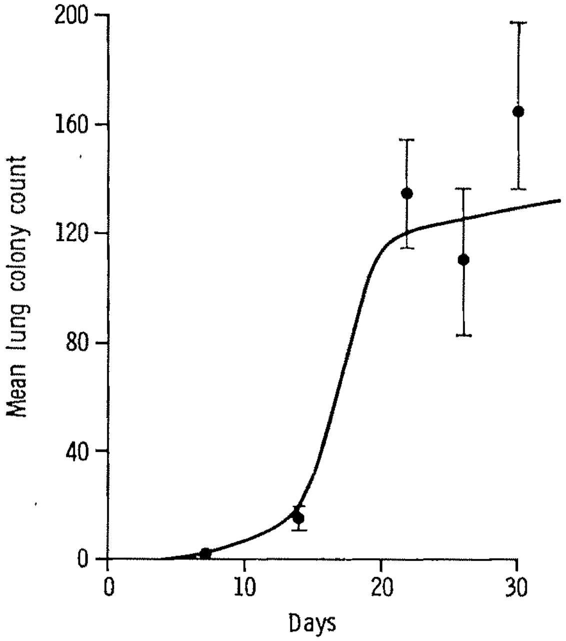

Fig. 3. The number of colonies on the lung surface at various times after the intravenous injection of $2{\cdot}5 \times 10^4$ viable HX34 cells.

lymph node and HX46 from a subcutaneous metastasis of malignant melanoma.

The tumours were grown subcutaneously in Ara-C-prepared mice and passaged every 3–4 weeks. Disaggregation was performed by finely chopping the tumour into tiny pieces under sterile conditions by the crossed scalpel technique. Culture medium (Ham's F12 with 15 per cent Special Bobby Calf Serum from Gibco-Biocult) was added to the homogenate and the suspended pieces pipetted into a sterile capped Falcon tube. The tube was shaken violently to dislodge cells and the cell suspension was removed by pipette and filtered through a sheet of polyester mesh (pore size 30 µm, Henry Simon, Stockport). The single cell suspension thus obtained was centrifuged so that a small pellet of cells lay at the bottom of the Falcon tube. The supernatant containing the debris was decanted away and the pellet of cells suspended in culture medium. Viability of cells was assessed by dye exclusion using Lissamine Green, and viable cells were counted on a haemocytometer. A known number of cells was injected into mice via the tail veins and after a growth period of 24–30 days the mice were killed by cervical dislocation and the lungs removed and fixed in Bouin's fixative for 48 h. The lobes of each lung were then dissected apart and the lung surface colonies counted by dissecting

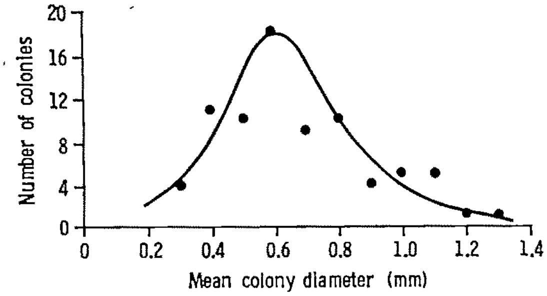

Fig. 4. Colony size distribution HX46 at day 30, after the intravenous injection of $4{\cdot}5 \times 10^4$ viable cells (78 colonies counted).

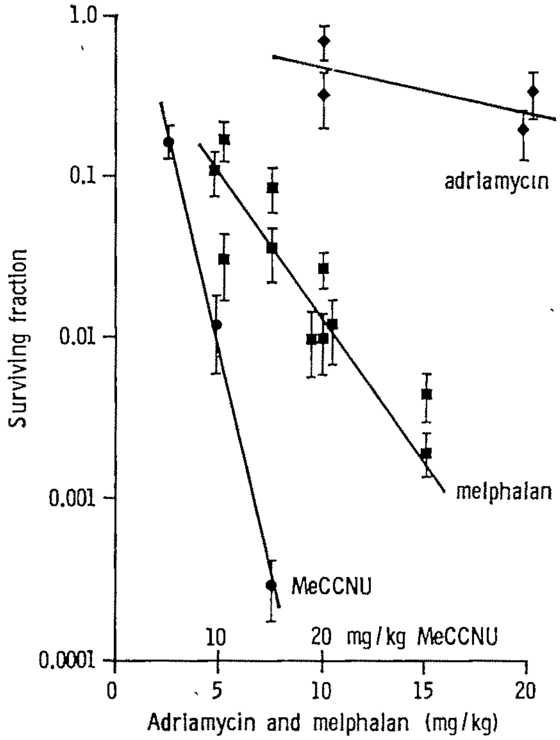

Fig. 5. Clonogenic cell survival curves of HX34 tumour following treatment with Adriamycin, melphalan and MeCCNU.

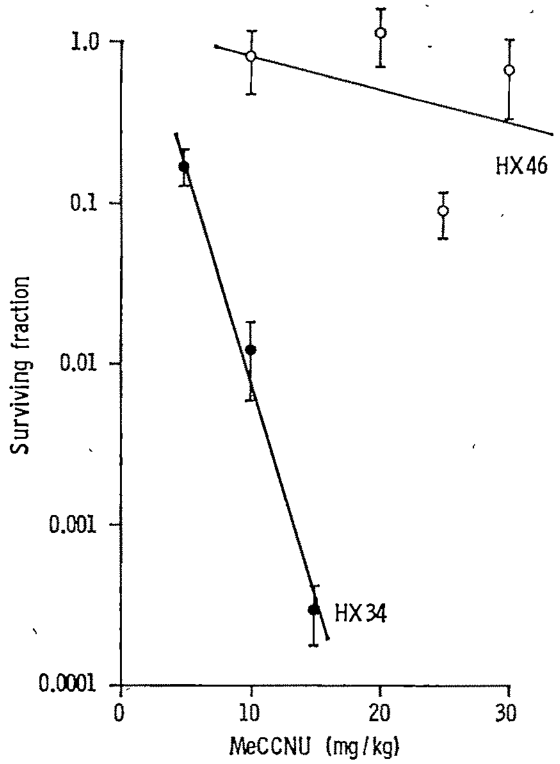

Fig. 6. Comparison of clonogenic cell survival curves of HX34 and HX46 following treatment with MeCCNU.

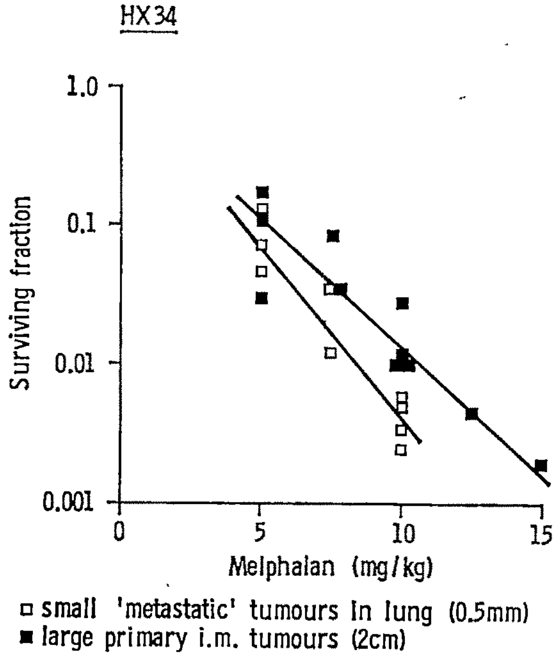

Fig. 7. Clonogenic cell survival curves for large intramuscular primary tumours (2 cm diameter) and small 'metastatic' tumours in the lung (0·5 mm diameter) following treatment with melphalan.

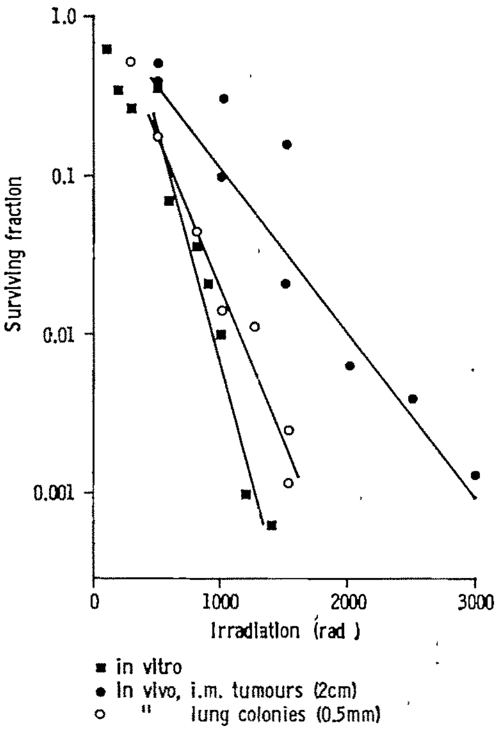

Fig. 8. Clonogenic cell survival curves of *in vivo* irradiated single cell suspension, *in vivo* irradiated intramuscular tumour (2 cm) and *in vivo* irradiated lung colonies (0·5 mm) (HX34).

microscope. The cloning efficiency (number of lung surface colonies divided by number of viable cells injected) for HX34 varied from 0·2 to 1 per cent and that of HX46 from 0·05 to 0·1 per cent.

The time at which colonies were scored following i.v. injection of viable cells varied with the growth rate of the tumours and was determined by time-course study (*Fig*. 3). The number of lung surface colonies at various times following injection of viable cells was determined and for HX34 there was evidence for a 'plateau' beyond approximately the twenty-first day. For HX46, a more slowly growing tumour, the 'plateau' was not reached until approximately the thirtieth day. An incubation period on the steep mid-portion of the curve was avoided and the exact day on the 'plateau' for terminating the assay was decided after colony size distribution studies (*Fig*. 4). For HX34 and HX46 these showed that at 24 and 30 days respectively there was a narrow distribution of colonies around a mode of 0·6 mm, which was a convenient diameter for counting by dissecting microscope.

Attempts were made to enhance cloning efficiency of viable cells by admixture of 10^6 plastic microspheres (15 μm, 3M Co. Ltd) or 10^6 lethally irradiated cells as described for experimental animal tumours (Hill and Bush, 1969; Hill and Stanley, 1975). The cloning efficiency was in fact reduced to one-third by either manoeuvre (Mann–Whitney, $P = 0{\cdot}014$; $P < 0{\cdot}002$ respectively) and was therefore not employed.

Chemosensitivity testing

Mice bearing subcutaneous or intramuscular tumours 1 cm in diameter were selected for study and the cytotoxic agent (Adriamycin, melphalan or MeCCNU (methyl 1,2-chloroethyl-3-cyclohexyl-1-nitrosourea)) was injected 18 h before assay in doses up to the LD_{10} (the dose lethal to 10 per cent of mice). In male CBA/lac mice of the Institute of Cancer Research colony the LD_{10} for Adriamycin and melphalan was about 15 mg/kg and for MeCCNU about 30 mg/kg. Control animals were included with each experiment. At least 6 mice were used for assay at each test point and the mean lung colony count at that test point determined. The cloning efficiency (CE) for control and test tumours was calculated:

$$\mathrm{CE}=\frac{\text{Mean colony count/lung}}{\text{No. viable cells injected i.v.}}$$

The surviving fraction (SF) of clonogenic cells following treatment by the test agent was calculated:

$$\mathrm{SF}=\frac{\text{CE test}}{\text{CE control}}$$

Initially a pilot experiment was performed at only one dose level but with a range of treated viable cell numbers. In this way, the approximate survival curve was derived. With this information a larger experiment was prepared with several dose levels, and the single cell suspension obtained from each of these diluted or concentrated as necessary to a final concentration that would provide an estimated countable number of lung colonies at each dose level. The greater the estimated cell kill, the larger the numbers of viable cells injected.

The data for clonogenic cell survival after treatment of HX34 (*Fig.* 5) were fitted with straight lines by linear regression analysis using the method of least squares and a computer program made available by Dr J. Millar. The lines were not constrained to go through the origin. The D_{10} (dose of drug required to achieve 1 log tumour cell kill) for Adriamycin (37·7 mg/kg) was significantly different ($P<0·01$) from that for melphalan (5·5 mg/kg) which was significantly different ($P<0·01$) from that for MeCCNU (4·25 mg/kg).

The data for treatment of HX34 and HX46 with MeCCNU (*Fig.* 6) show that the slope for HX34 ($D_{10}=4·25$ mg/kg) was significantly different ($P<0·01$) from that for HX46 ($D_{10}=59·5$ mg/kg).

Tumour size and response to chemotherapy

Cell survival in 2-cm diameter subcutaneous tumours and 0·5-mm diameter lung colonies (HX34) was compared following treatment with melphalan. Mice bearing lung colonies of 0·5 mm in diameter were prepared 3 weeks before assay by injecting sufficient viable cells to produce about 200 colonies. The mice were injected with intraperitoneal melphalan and, 18 h later, killed, and a single cell suspension of the lung colonies performed by finely chopping whole lungs and proceeding as previously described (*Fig.* 2).

The survival curves are illustrated in *Fig.* 7 and the slope of the survival curve for large i.m. tumours ($D_{10}=5·51$ mg/kg) is significantly different ($P<0·01$) from that for small lung colonies ($D_{10}=4·16$ mg/kg).

Tumour size and response to radiotherapy

Similarly, the clonogenic cell survival of 2-cm diameter subcutaneous tumours and 0·5-mm diameter lung colonies (HX34) was compared following single fraction irradiation (*in vivo*). Total body irradiation was used and no shielding of bone-marrow or gut was necessary as the animals were killed 18 h later for assay (*Fig.* 8).

Tumour cells are maximally radiosensitive when irradiated as a single cell suspension under fully oxygenated conditions and an *in vitro* survival curve was derived by irradiating a single cell suspension of HX34 prepared from untreated tumours (*Fig.* 8).

The slope of the exponential portion of the irradiation survival curve is expressed as that dose of irradiation (D_0) required to reduce survival to e^{-1} (37 per cent). The D_0 for *in vitro* irradiation was 144 rad; for *in vivo* irradiation of 0·5-mm lung colonies 220 rad and for 2-cm subcutaneous tumours 417 rad. The slopes of the three survival curves are statistically different ($0·01<P<0·05$).

The hypoxic fraction of the 2-cm diameter tumours was calculated to be 65 per cent on a multi-target equation assuming a mixed population of oxygenated and hypoxic cells in which the oxygenated cells were assumed to have the D_0 and n (extrapolation number) value of the lung colony survival curve and the hypoxic cells to have the D_0 of the 2-cm subcutaneous tumour.

Discussion

The lung colony assay for human malignant melanoma in immune-suppressed mice can be used to quantitate human tumour cell kill and may be useful in predicting clinical chemosensitivity. One melanoma (HX34) demonstrated a spectrum of chemosensitivity to three cytotoxic agents which broadly parallels the clinical experience with the same drugs in the treatment of disseminated melanoma. Adriamycin is regarded as having little activity while MeCCNU is considered to be one of the most effective agents in this situation. However, minimal tumour cell kill was achieved when HX46 was treated with MeCCNU, and it is interesting to note that the patient from whom HX46 was biopsied was treated with CCNU with no objective evidence of remission of disease.

A popular concept in cancer chemotherapy is that smaller tumours are more sensitive to chemotherapy (Frei, 1966; Schabel, 1975), and this concept has exerted an important influence on the design of some protocols of maintenance and adjuvant chemotherapy. The 'small is sensitive' theory is derived from the results of investigations on rodent tumours whose growth kinetics are greatly different from those of human tumours. Cytotoxic agents act mainly on proliferating cells and smaller rodent tumours with a better blood supply are more sensitive because of their higher growth fraction, shorter mean cell cycle time and better drug penetration. In the present investigation on a human melanoma, smaller tumours were again more sensitive but the difference in slopes of the survival curves was small. This finding is supported by the lack of clinical evidence of size-sensitivity to chemotherapy. If size is not an important determinant of response to chemotherapy, then it follows that chemotherapy may be most effective when tumour bulk is least and that adjuvant chemotherapy should be prescribed in maximum tolerated dose. Following the disappointing results of low-dose, short-course adjuvant chemotherapy, several trials have now been published where significant prolongation of the disease-free interval has followed intensive adjuvant chemotherapy (Bonadonna et al., 1976; Eilber et al., 1978; Pratt et al., 1978).

The importance of tumour size as a determinant of response to radiotherapy has long been recognized. It is likely that small tumour deposits are well vascularized, fully oxygenated and therefore relatively radiosensitive while large deposits have hypoxic cells associated with areas of necrosis and consequent reduced radiosensitivity. In the present study, a human melanoma 2 cm in diameter was shown to have a hypoxic fraction of about 65 per cent, which is greater than that reported for experimental animal tumours (Rockwell and Kallman, 1973; Shipley et al., 1975) or for a human pancreatic tumour (Courtenay et al., 1976). However, the slope of the *in vitro* survival curve was similar to that previously reported for *in vitro* irradiation of single cell suspensions of rodent tumours (Hill and Bush, 1969; Thompson and Rauth, 1974) and human tumours (Barranco et al., 1971; Thompson et al., 1975). This similarity of *in vitro* D_0 values for human and animal malignant cells supports the view that the main determinant of radiosensitivity or radioresistance is hypoxia in the *in vivo* environment. The clinical radioresistance of human malignant melanoma correlates well with the very large hypoxic fraction demonstrated in this study.

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I am grateful to Mr J.-C. Gazet for sponsoring this work for the Moynihan Prize.

Statistical note

The cell survival curve for mammalian cells described was derived by Lea (1946) and is given by:

$$SF = 1-(1-e^{-D/D_0})^n,$$

where SF is the surviving fraction, D is the dose to give this survival, D_0 is the negative reciprocal of slope on the exponential part of the curve on a semi-log plot and n is the extrapolation number.

To simplify calculations, this approximates to:

$$\log_e SF = \log_e n - D/D_0 \quad (\text{if } D > D_0)$$

and this latter formula was used here to calculate the values of slope, intercept and the errors on these by linear regression analysis as formulated in *Geigy Scientific Tables* (1970). The regression of $\log_e$ SF on dose D has been calculated by the method of least squares. This is to say that a straight line was established such that the sum of the squares of the vertical deviations of the given points from this line was a minimum.

Comparison of slopes for statistical significance

An F test (variance–ratio test) was done to see if the variances about both regression lines were similar. If so, a t value was calculated and the probability P obtained from tables (Bailey, 1959). If the variances were significantly different a d value was calculated as suggested by Bailey (1959) and again P obtained from tables.

References

BAILEY N. T. J. (1959) *Statistical Methods in Biology*, p. 98 and Appendix 2.

BARRANCO S. C., ROMSDAHL M. M. and HUMPHREY R. M. (1971) The radiation response of human malignant melanoma cells grown *in vitro*. *Cancer Res.* **31**, 830–833.

BONADONNA G., BRUSAMOLINO E., VALAGUSSA P. et al. (1976) Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N. Engl. J. Med.* **294**, 405–410.

BRADFORD PATTERSON W. (1968) Transplantation of human cancers to hamster cheek pouches. *Cancer Res.* **28**, 1637–1651.

CASTRO J. E. (1972) Human tumours grown in mice. *Nature (New Biol.)* **239**, 83–84.

COURTENAY V. D. and MILLS J. (1978) An *in vitro* colony assay for human tumours grown in immune-suppressed mice. *Br. J. Cancer* **37**, 261–268.

COURTENAY V. D., SMITH I. E., PECKHAM M. J. et al. (1976) *In vitro* and *in vivo* radio-sensitivity of human tumour cells obtained from a pancreatic carcinoma xenograft. *Nature (Lond.)* **263**, 771.

EILBER F. R., GRANT T. and MORTON D. L. (1978) Adjuvant therapy for osteosarcoma. *Cancer Treatment Rep.* **62**, 213–216.

FREI E. (1966) A commentary: selected considerations regarding chemotherapy as an adjuvant in cancer treatment. *Cancer Chemother. Rep.* **50**, 1–5.

GEIGY SCIENTIFIC TABLES (1970) Seventh edition. Macclesfield, Geigy Pharmaceuticals, p. 174.

HERMENS A. F. and BARENDSEN G. W. (1969) Changes of cell proliferation characteristics in a rat rhabdomyosarcoma before and after X-irradiation. *Eur. J. Cancer* **5**, 173–189.

HILL R. P. and BUSH R. S. (1969) A lung-colony assay to determine the radiosensitivity of the cells of a solid tumour. *Int. J. Radiat. Biol.* **15**, 435–444.

HILL R. P. and STANLEY J. A. (1975) The lung-colony assay: extension to the Lewis lung tumour and B16 melanoma. *Int. J. Radiat. Biol.* **27**, 377–387.

LEA D. E. (1946) *Actions of Radiations on Living Cells.* Cambridge, Cambridge University Press.

MILLAR J. L. (1976) Protective effect of cyclophosphamide or cytosine arabinoside pre-treatment on animals given a lethal dose of gamma irradiation. *Exp. Haematol.* **4**, 68. (Abstr.)

PRATT C. B., RIVERA G., SHANKS E. et al. (1978) Combined chemotherapy for osteosarcoma. *Cancer Treatment Rep.* **62**, 251–257.

ROCKWELL S. and KALLMAN R. F. (1973) Cellular radiosensitivity and tumour radiation response in the EMT6 tumour cell system. *Radiat. Res.* **53**, 281–294.

SCHABEL F. M. (1975) Concepts for systemic treatment of micrometastases. *Cancer* **35**, 15–24.

SHIMOSATO T., KANEYA T., MAGAI K. et al. (1976) Transplantation of human tumours in nude mice. *J. Natl Cancer Institute* **56**, 1251–1255.

SHIPLEY W. U., STANLEY J. A. and STEEL G. G. (1975) Tumour size dependency in the radiation response of Lewis lung carcinoma. *Cancer Res.* **35**, 2488–2493.

SMITH I. E., COURTENAY V. D. and GORDON M. Y. (1976) A colony forming assay for human tumour xenografts using agar in diffusion chambers. *Br. J. Cancer* **34**, 476–483.

STEEL G. G., COURTENAY V. D. and ROSTOM A. Y. (1978) Improved immune-suppression techniques for the xenografting of human tumours. *Br. J. Cancer* **37**, 224–230.

THOMSON J. E. and RAUTH A. M. (1974) An *in vitro* assay to measure the viability of KHT tumour cells not previously exposed to culture conditions. *Radiat. Res.* **58**, 262–276.

THOMSON L. F., SMITH A. R. and HUMPHREY R. M. (1975) The response of a human malignant melanoma cell line to high LET radiation. *Radiology* **117**, 155–158.

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The interpretation of mammographic ductal enlargement in cancerous breasts

R. E. MANSEL, I. H. GRAVELLE AND L. E. HUGHES*

SUMMARY

The xeromammograms of 128 women with breast cancer were coded radiologically according to Wolfe's gradings. The mastectomy specimens were then histologically examined for the presence of ductal abnormality.

The ducts were found to be normal in the cases coded as normal radiologically but they were not always abnormal histologically when considered to be abnormal radiologically. 'Ductal prominence' may be due to duct ectasia, intraduct hyperplasia or periductal collagenosis.

IF the best results are to be achieved in surgery for potentially curable breast cancer, early diagnosis is mandatory. A marker which either precedes the onset of invasive breast cancer or is detectable in high risk cases would allow very early diagnosis. According to Wolfe (1967, 1976) duct thickening visible on mammography is such a marker and women with prominent ducts or dense breasts on radiography have a higher risk of developing future breast cancer. Wolfe states that the increased radiodensity of prominent ducts is due to a periductal collagenosis, based on a study correlating radiology with pathology of excision biopsy specimens (Wellings and Wolfe, 1978).

A formal prospective study directed primarily at the subareolar ducts is needed since there are other possible causes of increased ductal density on mammography, such as duct ectasia. As it is not possible to obtain histological material on the whole group of patients with radiologically dense breasts, we have studied a consecutive group of cancer patients (with and without radiological duct abnormality) undergoing mastectomy.

Patients and methods

One hundred and twenty-eight consecutive unselected mastectomy specimens were examined radiologically and pathologically. The radiological examination consisted of routine preoperative xeromammography using the Rank Xerox System 125 taking xeromammograms in the craniocaudal and mediolateral planes (Gravelle and Hallett, 1975). The xeromammograms were read and classified on Wolfe's criteria by one radiologist (I. H. G.) without prior knowledge of the pathological results. Breasts with invisible ducts and little density were classified as N1 (normal); breasts with few visible ducts as P1 (minimal prominent duct pattern); those with many visible ducts as P2 (severe prominent duct pattern) (*Fig.* 1); and those breasts with generally increased density which obscured the underlying ductal pattern as DY (dense parenchyma/dysplasia pattern) (*Fig.* 2).

The pathological examination was carried out by sectioning the mastectomy specimens after the pathologist had taken his diagnostic blocks. The breasts were sliced to produce cross-sections of the subareolar ducts and sections for light microscopy were taken at three depths—0·5, 2 and 3 cm measured from the base of the nipple. These sections were stained with haematoxylin and eosin and examined by one of the authors (R. E. M.) who was unaware of the radiological classification at that time. The internal diameters of any ducts present were measured by using a calibrated eyepiece scale and the presence or absence of periductal collagenosis and intraductal hyperplasia were recorded. An internal ductal diameter exceeding 1 mm was selected to define the presence of duct ectasia.

Results

The numbers of mammograms in each of the four radiological subgroups are shown in *Table I*. As would be expected amongst cancer patients, few mammograms were classified as N1 and the commonest group was the severe prominent duct pattern or P2, which formed 53 per cent of the total. The incidence of periductal collagenosis and ductal dilatation in each radiological group is shown in *Table II*. Dilated ducts were not seen in the N1 breasts but were present in 32 per cent of P1 breasts, 33 per cent of P2 breasts and 39 per cent of DY breasts. Collagenosis was also absent in the N1 breasts but was found in 40 per cent of P1 breasts and in 53 per cent of P2 and DY breasts (some of these patients had both collagenosis and dilated ducts). Thus, approximately half of the breasts that showed increased ductal density radiologically were not found to have collagenosis of the subareolar ducts on histological examination. *Table III* gives the pathological findings in the 'no collagenosis' subgroup. Of the 15 such cases in the P1 group, 8 were shown to have either duct ectasia or intraduct hyperplasia which could explain the increased radiodensity, but in 7 breasts no histological cause for increased radiodensity could be found, thus giving a false positive radiological rate for the group as a whole of 28 per cent. Similarly the false positive rates for the P2 and DY groups were 13 and 11 per cent respectively.

Discussion

This study has shown that collagenosis is not invariably the cause of the prominent duct patterns in mammography. While the ducts are found to be normal when the radiologist reports them as such on mammography, they are not always abnormal histologically when they are considered to be abnormal by Wolfe's criteria. It seems clear from this study that duct ectasia and intraduct hyperplasia may cause the prominent duct pattern in a considerable percentage of cases. In a further small group (28 per cent in P1 and 13 per cent in P2) there is no obvious abnormality found on histological examination. The false positive rate amongst P1 cases is not altogether surprising, since it is not easy to separate the normal and P1 groups. However, the absence of histological abnormality in the P2 group is more difficult to explain. It is possible that in some cases the radiologically prominent ducts lie deeper in the breast than the subareolar region which we have studied histologically, and we are planning further studies of the whole breast to resolve this question. A further possibility is that in a number of cases the radiological appearance is primarily due to lobular abnormalities, as suggested by Wellings and Wolfe (1978).

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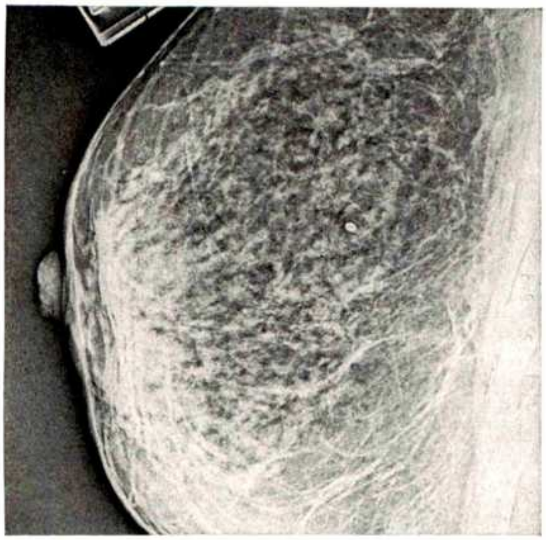

Fig. 1. Xeromammogram showing the severe prominent duct pattern (P2). The subareolar ducts can be seen as beaded linear opacities fanning out from the base of the nipple.

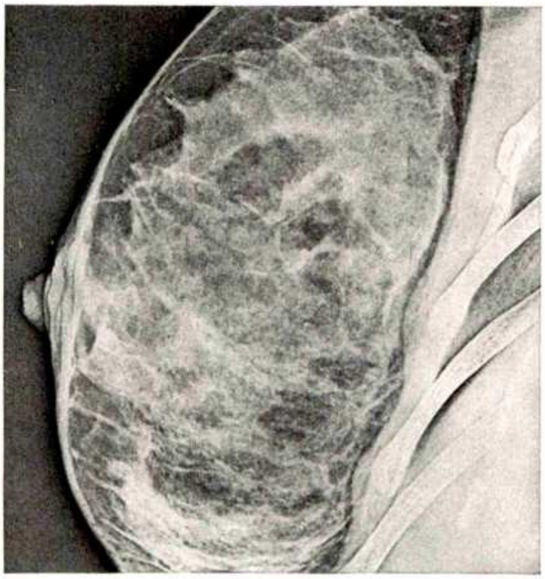

Fig. 2. Xeromammogram showing the dense parenchymal pattern (DY). The breast parenchyma is too dense to see any underlying subareolar duct pattern.

Table I: RADIOLOGICAL GROUPS

N1	Normal	6 (4%)
P1	Minor prominent duct pattern	25 (19%)
P2	Severe prominent duct pattern	69 (53%)
DY	Dysplasia pattern	28 (21%)
Total breasts		128

Table II: INCIDENCE OF DUCTAL DILATATION AND COLLAGENOSIS IN EACH RADIOLOGICAL SUBGROUP

	Dilated ducts > 1 mm	Collagenosis present
N1 ($n = 6$)	0	0
P1 ($n = 25$)	8 (32%)	10 (40%)
P2 ($n = 69$)	23 (33%)	37 (53%)
DY ($n = 28$)	11 (39%)	15 (53%)

Table III: HISTOLOGICAL FINDINGS IN THE RADIOLOGICALLY PROMINENT DUCTS SHOWING NO COLLAGENOSIS

P1 ($n = 15$)	5 Ectatic	
	3 Hyperplastic	
	7 Normal	(False positive rate 7/25 = 28%)
P2 ($n = 32$)	11 Ectatic	
	12 Hyperplastic	
	9 Normal	(False positive rate 9/69 = 13%)
DY ($n = 13$)	5 Ectatic	
	5 Hyperplastic	
	3 Normal	(False positive rate 3/28 = 11%)

The significance of histological collagenosis in relation to breast cancer is still in dispute, although it is accepted that there is frequently an association. Jackson and Orr (1957) reported finding a 70 per cent incidence of collagenosis in a detailed study of cancerous breasts and concluded that this feature in the presence of epithelial atypia should be regarded as pre-malignant. In contrast, Davies (1972), in a large study of both 'normal' post-mortem and cancerous breasts, found that the incidence of ductal hyperelastosis, obliteration and fibrous plaques was similar in both types of breast.

At the present time Wolfe's hypothesis of increased cancer risk associated with radiological duct abnormality is the subject of controversy. There are reports both substantiating (Krook, 1978) and disputing (Mendell et al., 1977) Wolfe's views. Direct correlation of pathological and radiological changes as reported here should lead to a greater appreciation of the spectrum of conditions which give rise to abnormal radiological findings. Hopefully this may lead to recognition of more specific radiological patterns, allowing better evaluation of Wolfe's hypothesis and better prediction of cancer risk.

Acknowledgements

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References

DAVIES J. D. (1973) Hyperelastosis, obliteration and fibrous plaques in major ducts of the human breast. *J. Pathol.* **110**, 13–26.

GRAVELLE I. H. and HALLETT P. (1975) Xeromammography—the process and image characteristics. *Med. Biol. Illust.* **25**, 93–96.

JACKSON J. G. and ORR J. W. (1957) The ducts of carcinomatous breasts with particular reference to connective tissue changes. *J. Pathol. Bacteriol.* **74**, 265–273.

KROOK P. M. (1978) Mammographic parenchymal patterns as risk indicators for incident cancer in a screening program: an extended analysis. *Am. J. Roentgenol.* **131**, 1031–1035.

MENDELL L., ROSENBLOOM M. and NAIMARK A. (1977) Are breast patterns a risk index for breast cancer? A reappraisal. *Am. J. Roentgenol.* **128**, 547.

WELLINGS S. R. and WOLFE J. N. (1978) Correlative studies of the histological and radiographic appearance of the breast parenchyma. *Radiology* **129**, 299–306.

WOLFE J. N. (1967) A study of breast parenchyma by mammography in the normal woman and those with benign and malignant disease. *Radiology* **89**, 201–205.

WOLFE J. N. (1976) Risk for breast cancer development determined by mammographic parenchymal pattern. *Cancer* **37**, 2486–2492.

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The value of measuring intravascular platelet aggregates in the prediction of postoperative pulmonary dysfunction

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SUMMARY

A modified Swank screen filter technique was used to investigate, first, whether intravascular platelet aggregates (IPA) could be detected in patients immediately after surgery and then, the relationship between IPA levels and postoperative pulmonary function. The test, as modified, achieved an excellent reproducibility ($r = 0{\cdot}95$) and a close correlation with the number of aggregates identified in samples of femoral vein blood by subsequent scanning electron microscopy ($r = 0{\cdot}93$).

In 20 patients IPA levels were measured 30 min and 3 h after surgery and pulmonary function (arterial Po_2, physiological dead space and alveolar/arterial Po_2 gradient) was evaluated preoperatively and on days 1 and 7 postoperatively. Patients with elevated IPA levels suffered a greater mean fall in arterial Po_2 at 7 days (1·8 kPa) than did patients with normal IPA levels (0·6 kPa) ($P < 0{\cdot}05$). This was explained by a marked increase in the pulmonary arteriovenous shunt as indicated by the alveolar/arterial Po_2 gradient (2·3 kPa v. 0·4 kPa, $P < 0{\cdot}01$). Those patients with increased pulmonary shunting and arterial hypoxia 1 week after surgery also had a greater fall in the platelet count on the first postoperative day.

The screen filtration technique is a reproducible test which measures IPA accurately and may be used to predict pulmonary function 1 week later. This suggests that treatment to inhibit IPA may reduce postoperative pulmonary dysfunction.

POSTOPERATIVE hypoxaemia is a well-recognized complication of surgery. In the immediate postoperative period it has been ascribed to the depressant effects of anaesthetics and analgesics, to pulmonary atelectasis, to inadequacies of blood volume and cardiac output in relation to tissue oxygen demand and to the effect of anaesthesia and postoperative pain on functional residual capacity in relation to closing volume (Bendixen et al., 1963; Kelman et al., 1967; Spence and Alexander, 1972). However, poor arterial oxygenation which continues beyond the immediate postoperative period, when these factors have ceased to apply, has not been adequately explained. This persistent hypoxaemia has many of the features of the condition known as post-traumatic pulmonary insufficiency or 'shock lung'; in both instances patients are hypoxaemic with normal or low arterial carbon dioxide tensions (Moore et al., 1969). McNamara et al. (1970) demonstrated, in battle casualties, a crude correlation between the severity of hypoxaemia and the volume of blood transfused. This was attributed to pulmonary sequestration of particulate matter in the transfusion with subsequent damage to the lung tissue. It has been suggested that, even without blood transfusion, a similar process may occur in shocked patients as a result of spontaneous platelet aggregation (Pardy and Dudley, 1977). However, as no method has yet been shown to measure circulating microaggregates *in vivo* reliably, their role in the development of pulmonary damage remains speculative.

Swank (1961) described the technique of screen filtration pressure (SFP) for the measurement of particulate matter in stored blood. We have modified and evaluated this technique as a means of measuring intravascular platelet aggregates (IPA) in postoperative patients. The relationship between these aggregates and pulmonary function following elective major surgery was then investigated.

Patients and methods

SFP technique

The screen filtration pressure technique (Swank et al., 1964) was modified to measure *in vivo* aggregates (*Fig.* 1). A nickel filter of 2·4-mm diameter and pore size 20 μm square and deep was primed by the passage of 5 ml of normal saline at 37 °C. The 5-ml test sample of blood was aspirated by femoral venepuncture into a plastic syringe and passed through the filter by a syringe pump at a constant flow rate of 0·4 ml/s. The pressure proximal to the filter was measured by a strain gauge transducer and recorded graphically as the SFP test curve. No anticoagulants were added and any sample which had not completed the test within 45 s of venepuncture was discarded. The filter was finally flushed with a further sample of saline and preserved in buffered 0·5 per cent gluteraldehyde prior to examination by scanning electron microscopy (SEM).

A scanning electron photomicrograph of the filter area was taken at a magnification of × 200. From this a count was made of the total number of pores completely obscured by aggregates, the maximum number of pores per field at this magnification being 140. These SEM counts were compared with various parameters such as the height and slope of the SFP curves.

SFP evaluation

The SFP recordings were performed within 30 min of surgery in 43 patients who had given informed consent. Preoperative values were measured in 36 patients to establish the normal range. Fourteen patients underwent 'minor' surgery and 29 'major' surgery necessitating elective or emergency laparotomy. The severity of 'major' surgery ranged from cholecystectomy to pancreaticoduodenectomy. In all cases general anaesthesia was used.

In 13 patients with elevated SFP, reproducibility was evaluated by repeating the test at the same time. To confirm that aggregates were forming *in vivo*, individual tests were duplicated, in 6 patients on each occasion, in the following ways: (*a*) at 30 and 45 s after venepuncture; (*b*) in blood sampled into two syringes, one primed with EDTA and one without; and (*c*) via collection of simultaneous samples from basilic and femoral veins.

Clinical study

Twenty patients about to undergo elective 'major' surgery gave written informed consent and formed the basis of the study.

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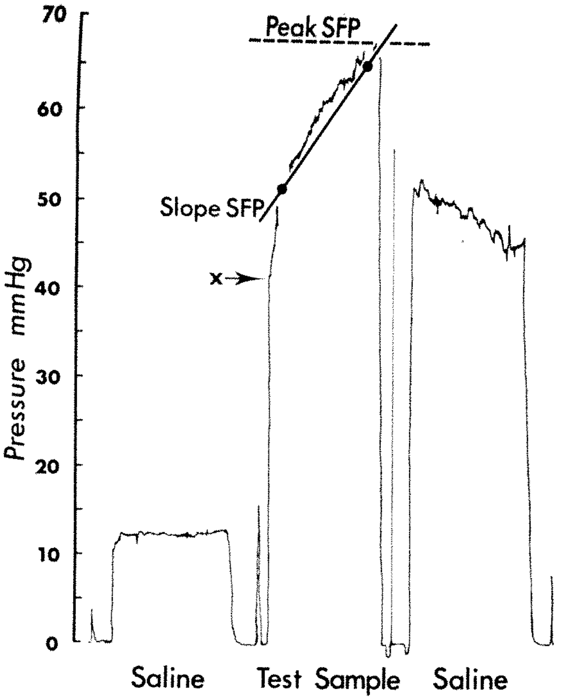

Fig. 1. The screen filtration pressure (SFP) waves produced by a sample of femoral vein blood, demonstrating peak SFP and the modified measurement of the SFP slope. Saline is passed before and after the test sample.

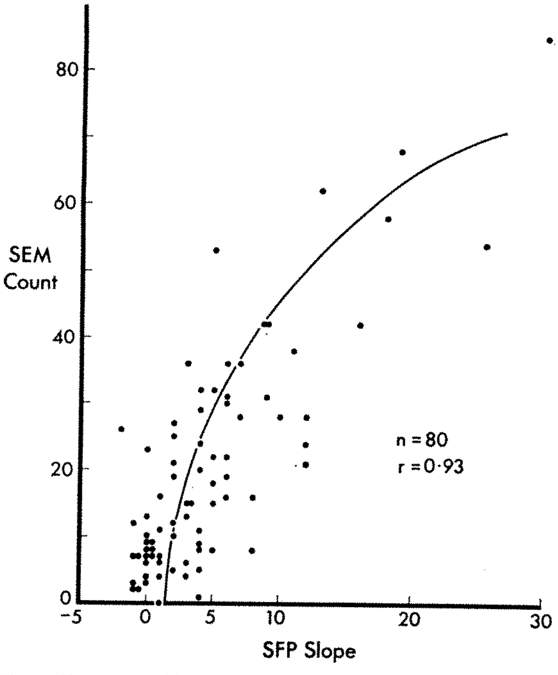

Fig. 2. The screen filtration pressure slope from 80 post-operative estimations correlates closely with the scanning electron microscopic count of the filter pores obscured by aggregates. The unit of SFP slope depends on recorder calibration; when multiplied by 0·214 it equals the pressure rise in mmHg/s.

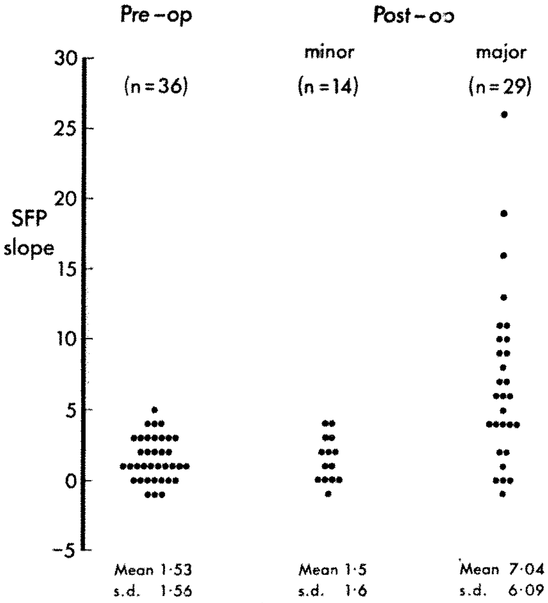

Fig. 3. Screen filtration pressure slopes in 43 patients before and within 30 min after surgery. The upper limit of normal is taken as 5 (*see* text). SFP slopes above this indicate the presence of intravascular platelet aggregates.

SFP was measured in femoral vein blood 30 min and 3 h post-operatively and, depending on the results, the patient was allocated to one of two groups—IPA-positive or IPA-negative.

Pulmonary function was evaluated preoperatively and post-operatively on days 1 and 7. Expired air was collected in a Douglas bag for a 5-min period. Arterial blood was taken simultaneously from the radial artery, through an indwelling parallel-sided 22-gauge Teflon cannula into a heparinized gas-tight syringe. Arterial $P\text{O}_2$, arterial $P\text{CO}_2$, expired $P\text{O}_2$ and expired $P\text{CO}_2$ were measured using gas electrodes. Alveolar $P\text{O}_2$ was calculated from the alveolar air equation of Filley et al. (1954) and physiological dead space from the Bohr equation (Bohr, 1891). All measurements were made in duplicate with the patient breathing room air. SFP estimations and pulmonary function measurements were performed by different investigators who compared results when the study was completed.

Detailed records were kept on other possible factors influencing pulmonary function, such as age, previous history of cardiopulmonary disease, smoking habits, medication, volume and nature of all intravenous infusions, together with serial changes in haemoglobin, white cell count and platelet count.

All operations were performed under general anaesthesia using intermittent positive pressure ventilation, nitrous oxide, oxygen and muscle relaxants being given with intravenous analgesia.

All statistical analyses were performed using the non-parametric Mann–Whitney U test.

Results

SFP evaluation

In 80 estimations, the correlation coefficient between peak SFP and the SEM count was 0·82. Although peak SFP is the parameter reported by previous investigators using this test, the slope of the SFP curve correlated more precisely, *r* equalling 0·93 in our patients (*Fig.* 2). This slope was measured from a point 2 s along the curve to a point 1 s prior to its termination, as interpretation of the initial point of this curve is subject to an unacceptable observer error (X in *Fig.* 1).

When the test was repeated at the same time in 13 postoperative patients, reproducibility was excellent ($r = 0{\cdot}95$). The SFP slope remained unaltered after a 15-s delay in performing the test (SFP at 30 s, mean 4·3, range 1–9; at 45 s, mean 4·6, range 0–8), and was not affected by the addition of EDTA to the syringe (SFP with EDTA, mean 5·7, range 0–12; without EDTA, mean 6·0, range 0–12). SFP was elevated only in femoral vein samples (mean 10·2) and not in samples taken simultaneously from the basilic vein (mean 1·4).

In 36 preoperative estimations and 14 following 'minor' surgery, the SFP slope remained below 5 in all but 1 (*Fig.* 3). However, in 29 patients following 'major' surgery, SFP elevation to greater than 5 was seen in 17. The mean SFP slope in this group was 7·1 ($\pm 6{\cdot}09$ s.d.), which is significantly higher than that after 'minor' surgery ($1{\cdot}5 \pm 1{\cdot}6$) or prior to operation ($1{\cdot}5 \pm 1{\cdot}56$, $P < 0{\cdot}001$). On this evidence intravascular platelet aggregates (IPA) were deemed to be present when SFP slopes were 5 or greater (mean preoperative $\text{SFP} + [2 \times \text{s.d.}] = 4{\cdot}7$).

Clinical study

Of the 20 patients in the clinical study, 10 proved to be IPA-negative (SFP slope <5) and 10 IPA-positive ($\text{SFP} > 5$). The mean sum of SFP at 30 min and 3 h was 2·4 (range −2 to 6) in the IPA-negative group, and 10·5 (range 6 to 24) in the IPA-positive patients. *Pulmonary function*: On the first postoperative day there was no difference between the two groups in any of the pulmonary function measurements (*Table I*). In the IPA-negative group mean preoperative arterial Po_2 (±s.e.mean) was 11·0 ($\pm 0{\cdot}55$) kPa and fell by 2·7 ($\pm 0{\cdot}48$) kPa on the first day after surgery. In the positive group this fall was 2·9 ($\pm 0{\cdot}36$) kPa. There was a wide scatter of change in physiological dead space (PDS) in the two groups, hence the mean rises of 4·1 ($\pm 19{\cdot}6$) ml in the IPA-negative group and 71·3 ($\pm 20{\cdot}1$) ml in the positive group were not significantly different. The rise in pulmonary arteriovenous shunt, denoted by the alveolar/arterial Po_2 gradient (A-ado$_2$), was marginally greater in patients with IPA ($2{\cdot}9 \pm 0{\cdot}66$ kPa) than in those without ($1{\cdot}9 \pm 0{\cdot}47$ kPa). This difference, however, was not significant.

One week after surgery the mean arterial Po_2 in the IPA-positive group was still 1·8 ($\pm 0{\cdot}38$) kPa below the preoperative value, whereas the mean arterial Po_2 in the IPA-negative group had recovered to only 0·6 kPa below its preoperative value. The difference between the two groups was statistically significant ($P < 0{\cdot}05$). The fall in arterial Po_2 in the IPA-positive group was due to an increase in pulmonary shunt, demonstrated by a rise in the alveolar/arterial oxygen gradient. The A-ado$_2$ rose from 3·8 ($\pm 0{\cdot}43$) kPa preoperatively to 6·1 ($\pm 0{\cdot}56$) kPa 1 week after surgery, a rise of 2·3 ($\pm 0{\cdot}43$) kPa or 61 per cent of the preoperative value. In the IPA-negative group the preoperative A-ado$_2$ of 4·3 ($\pm 0{\cdot}54$) kPa rose by only 0·4 ($\pm 0{\cdot}54$) kPa 1 week after surgery. This difference between the two groups was highly significant ($P < 0{\cdot}01$). The change in arterial Po_2 was not due to an alteration in the physiological dead space, which remained virtually unchanged in the two groups.

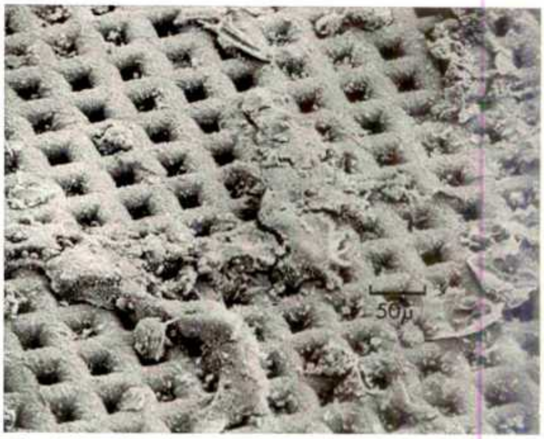

Fig. 4. Scanning electron micrography (× 150) of a filter from a patient whose SFP was elevated at 8, 30 min after colectomy.

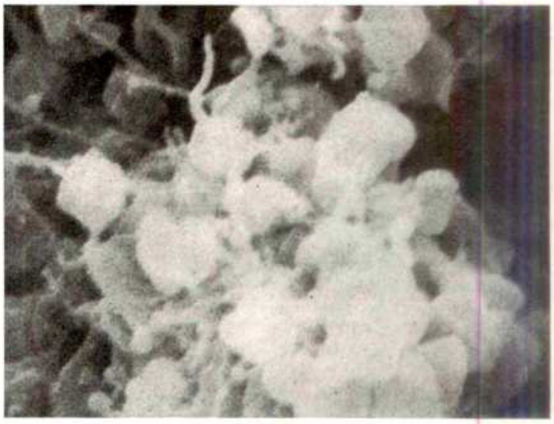

Fig. 5. Scanning electron micrograph (× 7 500) at high magnification showing the structure of an aggregate. The predominant cells are highly active platelets, which are developing pseudopodia and cystoplasmic links.

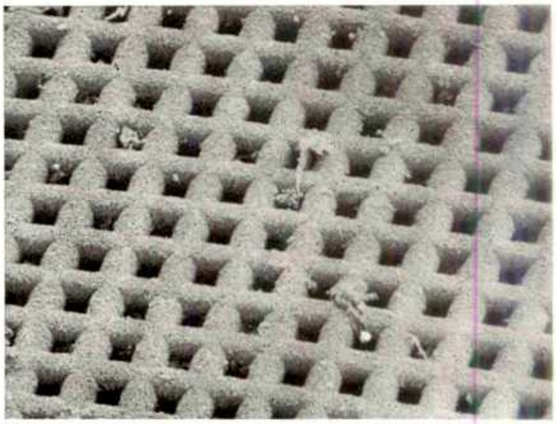

Fig. 6. Scanning electron micrograph (× 150) of a filter from a patient whose SFP was 1.

Table I: PULMONARY FUNCTION: PRE- AND POST-OPERATIVE MEAN AND STANDARD ERROR IN 20 PATIENTS WITH (IPA+ve) AND WITHOUT (IPA−ve) DETECTABLE INTRAVASCULAR AGGREGATES

Arterial Po_2 (kPa)		PDS (ml)		Alveolar/arterial Po_2 gradient (kPa)	
IPA−ve	IPA+ve	IPA−ve	IPA+ve	IPA−ve	IPA+ve
Preoperative					
11·0 ±0·55	10.8 ±0·46	164·3 ±25·5	182·9 ±17·5	4·3 ±0·54	3·8 ±0·43
Postoperative Day 1					
8·3 ±0·30	7·9 ±0·57	168·4 ±33·8	254·2 ±14·4	6·2 ±0·41	6·7 ±0·84
Postoperative Day 7					
10·4 ±0·47	9·0 ±0·53	152·4 ±19·0	193·4 ±22·0	4·7 ±0·31	6·1 ±0·56

PDS, Physiological dead space.

Table II: INCIDENCE OF OTHER FACTORS WHICH INFLUENCE PULMONARY FUNCTION COMPARED IN IPA+ve AND IPA−ve GROUPS

	IPA−ve	*P*	IPA+ve
Age >60 (mean age)	6 (56·1)	n.s.	5 (61·3)
Previous history of cardiopulmonary disease	3	n.s.	2
Cigarette smokers	5	n.s.	7
Received blood transfusion (mean volume l)	3 (1·6)	n.s.	6 (3·1)
Mean fall in Hb day 1(g/dl)	1·6	n.s.	1·6
Mean fall in platelet count day 1 (10^9/l)	21·4	$P<0{\cdot}02$	81·7

Scanning electron microscopy of the screen filters from the IPA-positive group demonstrated multiple adherent aggregates up to 300 μm in diameter (*Fig.* 4). The major bulk of these aggregates consisted of platelets that on high power microscopy can be seen to have undergone marked morphological change (*Fig.* 5). In the IPA-negative group the filter surfaces were either clear or demonstrated small individual aggregates (*Fig.* 6).

There was no significant difference between the two groups with respect to age, medication, smoking habits or pre-existing cardiopulmonary disease (*Table II*). Six of the IPA-positive group received blood transfusion as did 3 of the negative group. The postoperative fall in Pao_2 and rise in A-ado_2 in the 9 patients who were transfused was marginally greater than in the 11 patients who received no blood transfusion, but these changes did not achieve statistical significance. The mean platelet count, however, in the positive group fell by 81·7 × 10^9/l 1 day after surgery. This fall is significantly greater than the fall of 21·4 × 10^9/l observed in IPA-negative patients ($P<0{\cdot}025$). Mean platelet levels returned to preoperative values over the following week.

Discussion

Intravascular microaggregates have not previously been demonstrated, or implicated, in the aetiology of postoperative hypoxaemia. Their detection in patients undergoing elective procedures such as ulcer surgery and colon resection had not been anticipated, especially as there was little previous evidence, even in severe shock, that they ever formed in substantial numbers. It was possible to examine the occurrence of the aggregates and their effect on pulmonary function once the SFP methodology had been modified and shown, on clinical application, to be reproducible.

Previous application of the Swank technique to evaluate patients gave disappointing results, possibly as these studies were performed in the laboratory on anticoagulated blood. Heparin, for example, is known to stimulate platelet aggregation, whereas the disaggregation stimulated by EDTA has been used as a measure of *in vivo* microaggregates (Wu and Hoak, 1974; Zucker, 1974). In this study, the apparatus was constructed on a standard ward dressing trolley and estimations were performed at the bedside. Thus, immediate and easily interpreted results are readily available in any clinical situation. The SFP curve has usually been evaluated using peak SFP (Swank et al., 1964; Dhall et al., 1969; McNamara et al., 1970), which, although accurate *in vitro*, would be influenced by the changes in blood viscosity and red cell deformability that may follow surgery. In this study the objective was to measure only the aggregates in blood, and the slope of the test curve correlated most accurately with their detection by SEM.

The technique was carefully standardized to eliminate variables due to sampling procedures. In our opinion the following four observations confirmed that the aggregates measured arose within the venous system: (*a*) the fall in platelet count over the 24-h operative period was greater in patients who had an elevated SFP; (*b*) priming of the syringe with EDTA prior to venepuncture did not alter the value of the SFP slope; (*c*) the SFP was no greater at 45 s than it had been at 30 s after venepuncture; (*d*) SFP levels may be normal in the arm, when simultaneously elevated in the femoral vein blood. This latter finding also suggests that aggregates may only form in regions of the venous system where, as a result of vasoconstriction, stasis accompanied by poor tissue perfusion commonly occurs. The failure to detect these aggregates in arm veins must also indicate that they are removed effectively by one circulation through pulmonary and peripheral tissue. For this reason, elevation of SFP in femoral blood in our patients could not result from the infusion of stored blood, which in every case was given via the arm veins.

Painful wounds and respiratory depression by drugs are important causes of sputum retention, segmented atelectasis and decreased lung volume; all these mechanisms are therefore important in the aetiology of low arterial oxygen tensions on the first day following surgery. The causes of persistent hypoxaemia, however, are less well documented. Although microaggregates have not previously been implicated in this condition, they have been found in the lungs and tissue of patients who have died after massive injury (Blaisdell et al., 1970). It was postulated that aggregates arose by a process of intravascular aggregation as a result of tissue trauma, hypoperfusion and ischaemia with subsequent release of vasoactive substances and lysosomal proteases. We formed the impression in our study that microaggregate levels were elevated in those patients in whom peripheral vasoconstriction had produced clinically obvious hypoperfusion of the feet with cold ischaemic toes. Hence we suspect that the metabolic products of tissue ischaemia, possibly combined with venous stasis, may have triggered platelet aggregation.

Transfusion of stored blood is known to affect pulmonary function adversely but this relationship failed to reach statistical significance in the patients we studied. The relationship between intravascular aggregation and pulmonary arteriovenous shunting seen in our patients may conceivably be coincidental. However, Dedichen and Kordt (1974) showed that the venous return from the legs usually exceeds 30 l/h during general anaesthesia, suggesting that the volume of aggregates from this source could be expected to have a greater effect on the pulmonary circulation than transfused bank blood. Normally aggregates are filtered out by the reticuloendothelial system in the lung, but if reticuloendothelial activity were deficient or overwhelmed by massive microembolization, this could lead to that condition known, in appropriate circumstances, as 'shock lung' (Pardy and Dudley, 1977). Our results suggest that this process, in a less severe form, occurs in many surgical patients. It seems possible, therefore, that persistent postoperative hypoxaemia may represent one aspect of a pathological spectrum which in its most severe form presents as the adult respiratory distress syndrome.

Our results indicate that screen filtration pressure is a reproducible measure of intravascular microaggregates which may be used immediately after surgery to predict pulmonary function 1 week later. These findings give tangible support to the hypothesis that intravascular aggregation leads to pulmonary microembolization. The method described may be used to evaluate scientifically the importance of intravascular aggregation and establish therapeutic regimens which, by preventing aggregate formation, may conceivably reduce postoperative hypoxaemia.

Acknowledgements

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References

BENDIXEN H. H., HEDLEY-WHITE J. and LAVER M. B. (1963) Impaired oxygenation in surgical patients during general anaesthesia with controlled ventilation. *N. Engl. J. Med.* **269**, 991–996.

BLAISDELL F. W., LIM R. C. and STALLONE R. J. (1970) The mechanism of pulmonary damage following traumatic shock. *Surg. Gynecol. Obstet.* **130**, 15–22.

BOHR C. (1891) Ueber die Lungenathmung. *Skand. Arch. Phyysiol.* **2**, 236.

DEDICHEN H. and KORDT K. F. (1974) Blood flow in normal human ileofemoral arteries studied with electromagnetic technique. *Acta Chir. Scand.* **140**, 371–376.

DHALL D. P., ENGESET J., MCKENZIE F. N. et al. (1969) Screen filtration pressure of blood—an evaluation. *Cardiovasc. Res.* **3**, 147–154.

FILLEY G. F., MACINTOSH D. J. and WRIGHT G. W. (1954) Carbon-monoxide uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. *J. Clin. Invest.* **33**, 530–539.

KELMAN C. R., NUNN J. F., PRYS-ROBERTS C. et al. (1967) The influence of cardiac output on arterial oxygenation. A theoretical study. *Br. J. Anaesth.* **39**, 450–458.

MCNAMARA J. J., MOLOT M. D. and STREMPLE J. F. (1970) Screen filtration pressure in combat casualties. *Ann. Surg.* **172**, 334–341.

MOORE F. D., LYONS J. H., PIERCE E. C. et al. (1969) *Post-traumatic Pulmonary Insufficiency*. Philadelphia, Saunders.

PARDY B. J. and DUDLEY H. A. F. (1977) Post-traumatic pulmonary insufficiency. *Surg. Gynecol. Obstet.* **144**, 259–269.

SPENCE A. A. and ALEXANDER J. I. (1972) Mechanisms of postoperative hypoxaemia. *Proc. R. Soc. Med.* **65**, 12–14.

SWANK R. L. (1961) Alteration of blood on storage: measurement of adhesiveness of 'aging' platelets and leukocytes and their removal by filtration. *N. Engl. J. Med.* **265**, 728–733.

SWANK R. L., ROTH J. C. and JANSEN J. (1964) Screen filtration pressure method and adhesiveness and aggregation of blood cells. *J. Appl. Physiol.* **19**, 340–346.

WU K. K. and HOAK J. C. (1974) A new method for the quantitative detection of platelet aggregates in patients with arterial insufficiency. *Lancet* **3**, 924–926.

ZUCKER M. B. (1974) Effect of heparin on platelet function. *Thromb. Diath. Haemorrh.* **33**, 63–65.

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Regulation of enterokinase synthesis in animal and human small intestine by luminal signals: its implication in upper gastrointestinal surgery

N. J. BETT*

SUMMARY

Enterokinase is an enzyme produced by the mucosa of the small intestine. Its sole function is to activate trypsinogen to trypsin. In animals and man the duodenum and proximal jejunum have high levels of activity whereas the remaining small bowel has minimal levels.

A reproducible assay was developed for measuring mucosal enterokinase activity applicable to operative and endoscopic biopsies. Anaesthetic and operative techniques were developed for small intestinal resections in guinea-pigs to ensure their long term survival.

Transposition of high-enterokinase-secreting segments of guinea-pig small intestine to low-enterokinase regions and vice versa showed no alteration of enterokinase activity in the transposed segments. Similarly, resection of the enterokinase region in five proximal pancreaticoduodenectomy operations in man revealed no induction of enterokinase in the remaining jejunum at endoscopy 6 months later.

Isolation of high-enterokinase-secreting segments of small bowel from their luminal continuity by fashioning of Thiry–Vella fistulas led to a decay of enterokinase activity to minimal levels within 12–16 h. Perfusion of these fistulas with trypsin and sodium, or chymotrypsin and sodium, prevented this decay. If the enterokinase was allowed to decay over 24 h its activity could be restored to 80 per cent of its normal level by perfusion for 24 h with trypsin and sodium.

Trypsin and sodium act in combination on an enterocyte membrane receptor to stimulate enterokinase synthesis.

HEIDENHEIN showed in 1875 that freshly secreted pancreatic juice contains no active proteases. In 1900, Schepowalnikov, working in Pavlov's laboratory, discovered that pancreatic juice is activated by a duodenal factor which he named enterokinase. In 1939 Kunitz demonstrated that enterokinase is an enzyme which catalyses non-active trypsinogen to its active form—trypsin—by a first order reaction. A cascade reaction then occurs, as trypsin activates all the other proteolytic zymogens and prophospholipase in pancreatic juice. Without enterokinase therefore, the zymogens remain inactivated, digestion fails and protein starvation results (Hadorn et al., 1969).

Yamashina (1956) showed that enterokinase is a large glycoprotein (mol. wt $\simeq$ 200 000 : 30 per cent sugar) and that the activation of bovine trypsinogen was by hydrolysis of the peptide bond between lysine-6 and isoleucine-7, releasing active trypsin and its activation peptide Val-(Asp)$_4$-Lys.

Immunofluorescent studies using antiserum to pure human enterokinase have demonstrated its presence in man on the brush-border and glycocalyx of the enterocytes of the duodenum and proximal 10–20 cm of the jejunum (Hermon-Taylor et al., 1977).

This present study is designed to answer two questions. If the duodenum and proximal jejunum are removed, will enterokinase induction occur in the more distal small intestine and what factors control the mucosal synthesis of the enzyme?

Materials and methods

Mucosal enzyme assays

Enterokinase and aminopeptidase were assayed in 2–6-mg samples of fresh mucosa. After biopsy, the mucosal sample was washed in normal saline, gently blotted and weighed. For enterokinase it was immediately placed in 0·2 ml 70 mM Na succinate buffer, pH 5·6, containing 6·8 mM glycodeoxycholate (GDOC). Then 0·25 ml of a trypsinogen solution (1 mg/ml in 1 mM HCl with 2·2 mM CaCl$_2$) were added and the sample incubated for 30 min at 30 °C. The reaction was stopped by the addition of one drop of 2 M HCl. Of the supernatant, 0·2 ml were assayed for trypsin using N-α-benzoyl-L-arginine ethyl-ester (BAEE) (Baratti et al., 1973). Specific enterokinase activity was expressed as pmol trypsin min^{-1} mg^{-1}.

For aminopeptidase the fresh weighed biopsy was placed directly in 1 ml 50 mM Na phosphate buffer, pH 7·2, to which 0·1 ml of 16·6 mM leucine-p-nitroanilide (LPNA) was added. Incubation was for 15 min at 30 °C when the reaction was stopped with one drop 2 M HCl and the supernatant read spectrophotometrically at Δ_{405}. Specific aminopeptidase activity was expressed as pmol nitroanilide min^{-1} mg^{-1}.

Operative survival of guinea-pigs

Preliminary studies carried out with small intestinal biopsies from rats, rabbits, guinea-pigs, dogs and cats showed that the small intestinal enterokinase profile of guinea-pigs bore the closest resemblance to man. Unlike the rat it is difficult to carry out small intestinal resection and anastomosis in guinea-pigs and ensure long term survival. The following operative and anaesthetic details were found to be essential: SPF guinea-pigs must be used; 100 μg atropine 1 h before operation and repeated tracheal suction throughout; induction and maintenance of anaesthesia with 2 per cent methoxyflurane (3 l/min O$_2$+N$_2$O); monitoring and maintenance of body temperature at 38·5–40 °C during operation and afterwards until fully mobile; N saline 5 ml kg^{-1} h^{-1} s.c. Unlike in the rat, guinea-pig small intestine is fragile and anastomoses had to be performed using interrupted 6/0 chromic catgut sutures 1 mm apart everting the mucosa.

Studies using guinea-pigs

In 3 guinea-pigs the enterokinase and aminopeptidase profiles in the small intestine were established by multiple biopsies. In each of 6 guinea-pigs a 5-cm length of low-enterokinase-containing distal small intestine was transposed on its intact mesentery to the proximal high-enterokinase-secreting region. Enzyme levels were established in short segments from both ends of the transposed segment at the donor site and at the site of insertion. The animals were allowed to recover and were sacrificed at 3 months. A 5-cm segment of high-enterokinase-secreting proximal intestine was transposed to a distal low region in an identical manner in a further 6 animals; in both groups small intestinal enzyme profiles were measured after 3 months.

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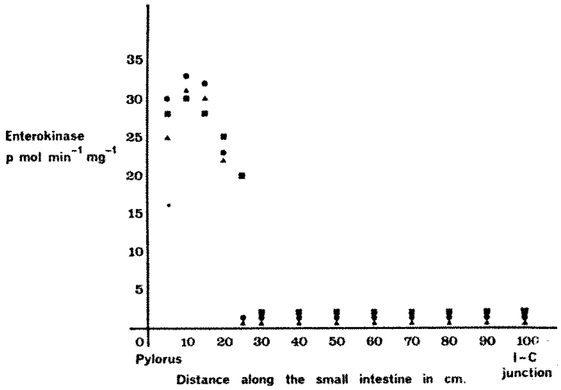

Fig. 1. Enterokinase activity along the small intestine of 3 guinea-pigs.

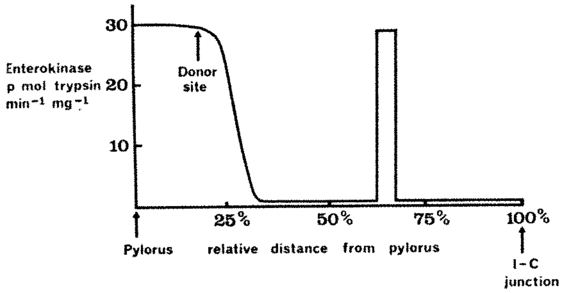

Fig. 2. Small intestinal enterokinase profile in the guinea-pig 3 months after transposition of a low-enterokinase-secreting segment of small intestine to a high-enterokinase region.

In a third group of 6 animals a 5-cm high-enterokinase-secreting segment was isolated from luminal continuity on its intact mesentery and brought to the anterior abdominal wall as a Thiry–Vella fistula. Enzyme levels were measured from both ends of the isolated segment at operation and after sacrifice 3 months later. In a further group of short term studies mucosal enterokinase and aminopeptidase levels were measured in Thiry–Vella loops of high-enterokinase segments at increasing intervals following isolation. Finally 24-h luminal perfusion of the isolated loops was carried out *in vivo* in a series of animals to identify factors which might affect mucosal enterokinase activity.

Clinical studies

Mucosal enterokinase and aminopeptidase levels were determined in the duodenum, and in the jejunum just beyond the site of division, in 5 patients during proximal pancreaticoduodenectomy for periampullary tumours. Enzyme levels in the afferent loops were also determined in these patients and in endoscopic biopsies 6 months later.

Results

The profile of mucosal enterokinase activity throughout the small intestine in 3 guinea-pigs is shown in *Fig.* 1. The length of the high-enterokinase-secreting segment was sharply localized to the proximal 20 cm distal to the pylorus; the mean maximal enterokinase activity in this segment was 27·5 ± 1·4 (s.d.). Enterokinase activity was always detected in the mucosa of the distal intestine but in the range 0·1–1·6 pmol trypsin min^{-1} mg^{-1} (pmT). In the same 3 animals aminopeptidase activity was evenly distributed throughout the small intestine; the range in each animal respectively being 0·87–1·37, 0·41–0·83 and 0·43–1·10 pmol nitroanilide min^{-1} mg^{-1} (pmN).

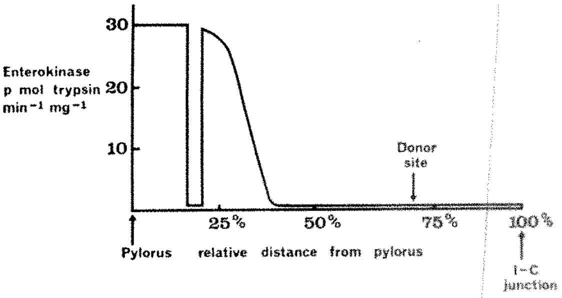

Fig. 3. Small intestinal enterokinase profile in the guinea-pig 3 months after transposition of a high-enterokinase-secreting segment of small intestine to a low-enterokinase region.

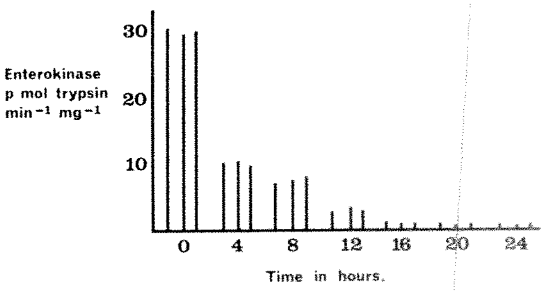

Fig. 4. Decline of mucosal enterokinase activity after *in vivo* isolation of an enterokinase-secreting segment of small intestine from luminal continuity.

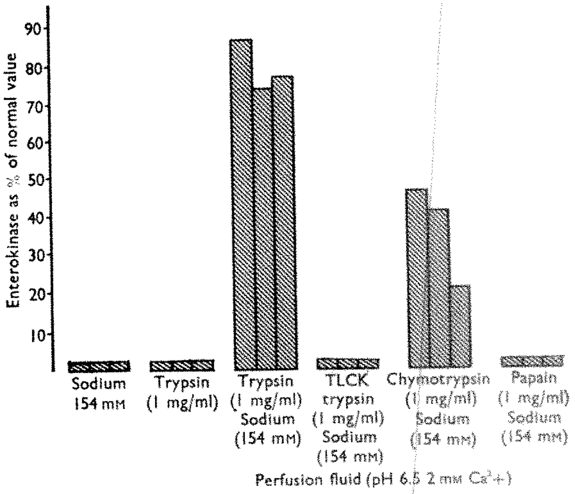

Fig. 5. Restoration of mucosal enterokinase after 24-h luminal perfusion *in vivo* of isolated duodenal–jejunal loops in the guinea-pig.

The enterokinase levels in the proximally transposed segment of distal intestine in each of the 6 healthy animals at, and 3 months after, operation were 1·5 : 0·7, 2·6 : 1·8, 0·8 : 0·6, 0·3 : 0·4, 0·6 : 0·5 and 0·6 : 0·3 pmT respectively. The mean aminopeptidase

Table I: EFFECT OF LUMINAL PERFUSION *IN VIVO* ON THE MAINTENANCE OF ENTEROKINASE SECRETION IN ISOLATED DUODENAL–JEJUNAL SEGMENTS

<10	20–50	70–100
No infusion	N saline, pH 6	Trypsin 1 mg/ml, 154 mM Na^+, 2 mM Ca^{2+}, pH 6·5
Water	N saline, pH 7	
Water + 2 mM Ca^{2+}	N saline, pH 8	
Val-(Asp)$_4$-Lys, 3 μg/ml	154 mM Na acetate	Chymotrypsin 1 mg/ml, 154 mM Na^+, 2 mM Ca^{2+}, pH 6·5
Albumin, 1 mg/ml	Trypsin 1 mg/ml + 2 mM Ca^{2+}	
10 mM GDOC		
10 mM KCL	Chymotrypsin 1 mg/ml + 2 mM Ca^{2+}	
5 mM essential amino acids		
TLCK trypsin, 1 mg/ml		
Autolysed trypsin, 1 mg/ml		

Values for enterokinase are given as a percentage of normal value.

Table II: MUCOSAL ENTEROKINASE AND AMINOPEPTIDASE LEVELS AT PROXIMAL PANCREATICODUODENECTOMY AND ENDOSCOPY 6 MONTHS LATER

Patient/sex and age	Duodenum		Jejunum		Jejunum 6 mth later	
	EK	AP	EK	AP	EK	AP
A. F./F (61 yr)	15·8	1·8	4·2	1·6	2·4	0·9
	16·5	1·3	3·4	2·2	0·8	0·9
	18·1	1·9	3·6	1·7	0·4	1·1
J. J./M (37 yr)	7·6	0·6	1·0	0·4	1·0	0·8
	6·8	0·6	0·5	0·4	0·3	0·7
	7·9	0·6	1·0	0·4	0·3	0·7
I. S. F/(65 yr)	11·5	0·5	0·8	0·8	0·0	0·6
	11·4	0·5	0·6	0·8	0·4	0·7
	9·6	0·6	0·8	0·8	0·6	0·7
J. G./F (52 yr)	5·8	0·6	1·8	0·7	1·7	0·6
	5·7	0·6	2·2	0·6	1·4	0·5
	6·1	0·6	2·0	0·6	1·6	0·5
C. L./M (75 yr)	6·5	0·7	1·7	1·1	0·3	0·5
	7·4	0·7	2·0	0·9	0·4	0·6
	7·2	0·7	1·8	1·2	0·2	0·7

All values are expressed as pmol min^{-1} mg^{-1}.
EK, Enterokinase; AP, aminopeptidase.

level in the segments before transposition was 0·58 ± 0·11 (s.d.) pmN and 0·48 ± 0·18 (s.d.) pmN 3 months later. The difference was not significant (*Fig.* 2).

The enterokinase levels in the distally transposed segments of proximal intestine in each of the 6 healthy animals at, and 3 months after, operation were 22·6 : 21·3, 31·0 : 30·0, 14·7 : 12·5, 22·6 : 19·7, 11·7 : 7·0 and 13·1 : 10·2 pmT respectively. The mean aminopeptidase level in the segments before transposition was 0·70 ± 0·19 (s.d.) pmN and 0·57 ± 0·17 (s.d.) pmN 3 months later. The difference was not significant (*Fig.* 3).

The enterokinase levels in the proximal small intestinal segments in each of the 6 healthy animals at, and 3 months after, isolation from luminal continuity were 12·1 : 1·0, 23·9 : 0·8, 18·8 : 1·1, 15·8 : 1·0, 19·7 : 1·3, 23·8 : 0·9 pmT. The mean aminopeptidase level in the segments before isolation was 0·63 ± 0·32 (s.d.) pmN and 3 months later 0·45 ± 0·14 (s.d.) pmN; the difference was not significant.

The time course of the decay of enterokinase activity in proximal small intestinal loops in 21 guinea-pigs at increasing intervals of time after isolation is shown in *Fig.* 4. Enterokinase activity fell to basal levels (0·4–2·2 pmT) by 16 h; aminopeptidase levels remained within the normal range. *Table I* shows that the decay in enterokinase activity was delayed by 24-h luminal perfusion *in vivo* of the isolated loops with solutions containing sodium ion, trypsin and chymotrypsin (Ca^{2+} was itself without effect but was included to prevent trypsin degradation). Perfusion with trypsin (1 mg/ml) and sodium (154 mM) in combination maintained enterokinase activity within its normal range. *Fig.* 5 shows that mucosal enterokinase activity in the isolated loops could be restored, after fall to basal levels, by 24-h luminal perfusion with a combination of trypsin and sodium, but not if the trypsin, although intact, was inactivated by TLCK* and not by trypsin or sodium alone. Chymotrypsin and sodium had an intermediate action on the restoration of enterokinase activity but papain and sodium was without effect.

Table II shows the enterokinase and aminopeptidase levels in three mucosal biopsies from the duodenum and divided jejunum at the time of proximal pancreaticoduodenectomy for periampullary tumour in 5 patients, and at endoscopic follow-up 6 months later. There was no increase in mucosal enterokinase activity in the remaining proximal jejunum.

Discussion

Assays similar to the ones described for the quantification of mucosal enterokinase have been used by other workers for the measurement of brush-border enzymes (Nordstrom and Dahlquist, 1971; Hadorn et al., 1974). The assay conditions described in the present study measured total available enterokinase since the majority of the enterokinase activity was present in the supernatant after incubation and transfer of the same mucosal sample to a second incubate showed minimal enterokinase activity. Furthermore, it has been pointed out by Scott et al. (1977) that the specific activities of other mucosal enzymes are best expressed per wet weight of fresh mucosa. The estimation of enterokinase in mucosal samples snap-frozen in liquid nitrogen and stored at −70 °C was inconsistent and all assays were carried out on fresh mucosa.

In the formation of Thiry–Vella fistulas Fabri et al. (1977) reported the survival of 4 out of 7 guinea-pigs. The difficulty of ensuring long term survival in guinea-pigs after intestinal resection is reflected in the paucity of reports on this subject in the literature. The initial mortality in intestinal resections which preceded the definitive ones in the present study was nearly 100 per cent; practice and the meticulous application of the perioperative and anaesthetic factors described, however, converted this to consistent near-total survival.

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* Tosyl-Lysyl-Chloromethyl ketone (Sigma Chemical Co.).

The results in guinea-pigs are in close agreement with the clinical findings and show that enterokinase induction does not occur in the more distal small intestine when transposed to the environment of a high-enterokinase-secreting region. Maximum enterokinase secretion is maintained in the proximal intestinal segments in luminal continuity with the distal small intestine. Since one-day old guinea-pigs have an adult-type enterokinase profile, these findings suggest that a maximum permissible level of enterokinase synthesis at any site in intact small intestine is established in intrauterine life.

The maintenance of aminopeptidase levels in the normal range in isolated proximal small intestinal loops suggests that the rapid decline of enterokinase activity under these circumstances is not an artefact of surgical transposition. The enterokinase decay time of 12–16 h is in agreement with the reported rate of protein macromolecular turnover in intestinal mucosa (Alpers, 1977). The results of the perfusion studies suggest that maximal enterokinase synthesis by the mucosa is dependent upon a continued cooperative interaction of luminal trypsin and sodium ion. Further experiments are being designed to elucidate the molecular events responsible for this signalling mechanism. Whatever their complexities, it is clear that if the high-enterokinase-secreting segment of small intestine is removed, enterokinase will not grow back.

Acknowledgements

I would like to thank Professor J. Hermon-Taylor, Dr D. A. W. Grant and Mr A. I. Magee for their invaluable advice and assistance, Miss S. Whitford for preparing the manuscript and Miss P. Maxwell-Allen for the illustrations.

References

ALPERS D. H. (1977) Protein turnover in intestinal mucosal villus and crypt brush-border enzymes. *Biochem. Biophys. Res. Commun.* 75, 130–135.

BARATTI J., MAROUX S. and LOUVARD D. (1973) Effect of ionic strength and calcium ions on the activation of trypsinogen by enterokinase. A modified test for the quantitative evaluation of this enzyme. *Biochim. Biophys. Acta* **321**, 632–638.

FABRI P. J., SCOTT B. C. and NELSON E. W. (1977) An *in vivo* preparation (Thiry–Vella fistula) suitable for the measurement of intestinal absorption in the guinea-pig. *Lab. Anim. Sci.* 27, 687–689.

HADORN B., HESS J., TROESCH V. et al. (1974) Role of bile acids in the activation of trypsinogen by enterokinase: disturbance of trypsinogen activation in patients with intrahepatic biliary atresia. *Gastroenterology* 66, 548–558.

HADORN B., TARLOW M. J., LLOYD J. K. et al. (1969) Intestinal enterokinase deficiency. *Lancet* 1, 812–813.

HERMON-TAYLOR J., PERRIN J., GRANT D. A. W. et al. (1977) Immunofluorescent localisation of enterokinase in human small intestine. *Gut* **18**, 259–265.

NORDSTROM C. and DAHLQUIST A. (1971) Rat enterokinase: the effect of ions and the localisation in the intestine. *Biochim. Biophys. Acta* 242, 209–225.

SCOTT B. B., SAIRMAN M. J., TOOTHILL C. et al. (1977) The expression of enzyme activity of biopsy tissue from the small intestine. *Digestion* 15, 182–187.

YAMASHINA I. (1956) The action of enterokinase on trypsinogen. *Acta. Chem. Scand.* **10**, 739–743.

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SHORT PAPERS

Three further short papers read at the meeting will be published subsequently: 'The preoperative detection of internal mammary lymph node metastases in breast cancer' by M. P. Osborne and I. Burn; 'Emergency treatment of variceal haemorrhage' by S. Sagar, I. D. Harrison, R. Brearley and R. Shields; 'The traumatic effect of the vascular clamp' by J. G. Harvey and M. Gough.

Plasma exchange and Raynaud's phenomenon—its assessment by Doppler ultrasound velocimetry

M. J. G. O'REILLY, A. J. DODDS, V. C. ROBERTS AND L. T. COTTON*

SUMMARY

In a group of 47 patients with Raynaud's phenomenon, Doppler ultrasound velocimetry was used to establish the severity of the disease by detecting the patency of the digital arteries. In conjunction with small digital occlusion cuffs, digital artery systolic pressure was measured on either side of the finger. A significant variation in systolic pressure was detected in each finger, and on each side of individual fingers. A more sensitive index of the severity of the disease was noted when the digital systolic pressure was compared to the brachial systolic pressure.

Plasma exchange, a potent method of lowering whole blood viscosity and plasma fibrinogen, was used to treat 18 of these patients. There was a significant improvement in digital vessel patency at both 21 °C and 13 °C after plasma exchange. Both the digital artery systolic pressure and the pressure index improved significantly after treatment.

As a result of the frequently reported incidence of raised blood viscosity (Pringle et al., 1965) and elevated fibrinogen levels (Jarrett et al., 1978) in patients with severe Raynaud's phenomenon, a rational method of treatment of these patients was considered to be plasma exchange which is known to reduce acutely blood viscosity and plasma fibrinogen (Pinching, 1978). Following the report of a pilot study (Talpos et al., 1978), a controlled trial was established to study the results of treatment in a group of patients with severe Raynaud's phenomenon.

Although plethysmography (Coffman and Cohen, 1971), arteriography (Downs et al., 1975) and isotope angiology (Hurlow and Strachan, 1978) have been reported as suitable methods of investigating the symptoms of patients with severe Raynaud's phenomenon, they may not accurately determine the degree of patency of the digital arteries. We determined to use Doppler ultrasound velocimetry following the report of Yao and his colleagues (1972) for, as Lewis (1929) had indicated: 'The signs and symptoms of Raynaud's phenomenon are a secondary manifestation of the abnormal sensitivity of the *digital arteries* to cold.' Doppler techniques are uniquely capable of detecting patency in individual vessels. In addition, with this technique, the patency of those digital vessels can be assessed under a variety of thermal stresses. Furthermore, the work of Nielsen and Lassen (1977), Lassen et al. (1977) and others has emphasized the importance, in these patients, of the intraluminal systolic pressure. This they measured plethysmographically. An alternative technique is to use the Doppler principle, with which the individual arteries can be directly insonated. The returning arterial flow, following release of a proximal occlusion cuff, can be immediately detected and the pressure at which this occurs (which is the digital artery systolic pressure) read from a mercury column.

Patients and methods

Forty-seven patients with severe Raynaud's phenomenon have been studied. Eight patients had severe digital ulcerations; 4 were known to have had digital ulcers which healed before treatment began. All patients were examined, lightly clothed, in a temperature-controlled laboratory at 20±1 °C.

After resting for 20–30 min, the fingers were insonated with a 10 MHz probe connected to an ultrasonic Doppler velocimeter. Insonation proceeded from proximal to distal phalange, on both the radial and ulnar sides of the finger. Each finger was considered as having available for insonation 6 digital artery segments, 3 radial, 3 ulnar. In both hands 56 digital artery segments were thus available for insonation. By counting the number of patent digital segments (i.e. those producing an audible Doppler shift on insonation), an estimate of the severity of the phenomenon in each patient could be obtained. This examination was then repeated after immersion of the hands for 1 min in water at 13 °C. Thus, following each of the temperature stresses, the number of patent digital arteries was obtained. This examination was repeated at 3-monthly intervals until a 9-month follow-up was reached.

Digital artery systolic pressure was also measured after each of the thermal stresses. A fine plastic (3-cm wide) cuff was placed around the proximal phalange. The digital artery on the radial side of the finger was insonated and the cuff inflated to suprasystolic levels. On cuff deflation, the returning arterial flow produced an audible Doppler shift readily detected by the probe. This procedure was repeated on the ulnar side of the finger and then for each of the fingers. This technique was also used to measure digital systolic pressure after each thermal stress. By comparing the digital systolic pressure to the brachial pressure (measured at the same time as the digital), a digital pressure index was obtained. A group of 10 normal control patients was examined in a similar manner on three occasions.

Eighteen patients were subjected to plasma exchange at weekly intervals for 4 to 5 weeks, 2·0–2·5 l of plasma being exchanged with equal amounts of purified protein fraction (PPF) and Haemaccel (Hoechst). Patients had blood removed before, after and mid-way between succeeding exchanges in order that blood viscosity, red cell deformability and plasma fibrinogen could be estimated.

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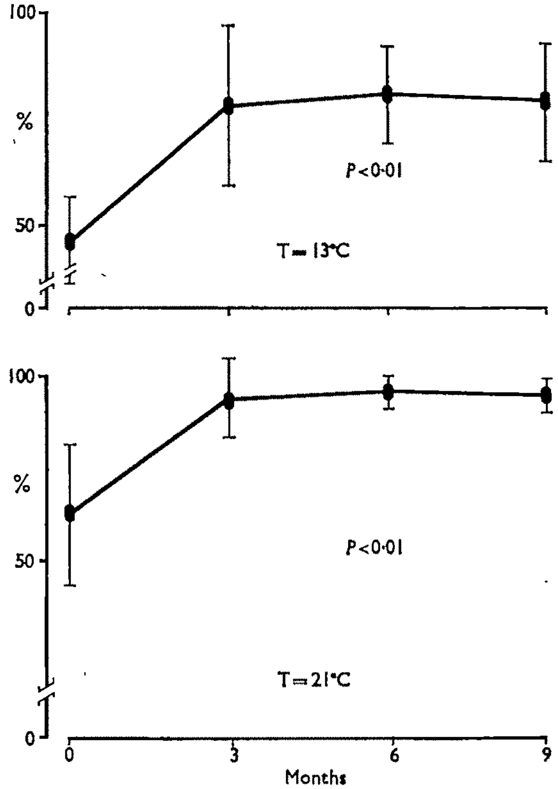

Fig. 1. Improvement in digital artery patency (per cent) after plasma exchange at 9-month review. Time 0 months indicates pre-treatment values.

Results

Using this technique of enumerating digital arteries we have found (*Fig.* 1) that the digital vessel patency (per cent) at 21 °C following plasma exchange improves from 63 per cent to 89 per cent at 9-month follow-up. Similarly, at 13 °C, the digital vessel patency improved from 46 per cent to 78 per cent. In both cases, this improvement was significant ($P<0{\cdot}01$ Student's t). In a group of 27 patients with Raynaud's phenomenon, the brachial systolic pressure was 131·0 ± 26·0 mmHg as compared to that in the control group of 115 ± 16·3 mmHg. These values were not significantly different. Before treatment, the digital pressure index at both 21 °C (*Fig.* 2) and at 13 °C (*Fig.* 3) was significantly lower than in the control group. Furthermore, it is noteworthy (*Fig.* 3) that at each temperature, the digital pressure index corresponding to both sides of the thumb was frequently less than in either the second, third or fourth fingers and similar to that of the fifth. The digital systolic pressure in all patients was less than in the control groups at 21 °C (*Fig.* 4) and the mean systolic pressure in the middle three fingers was always greater than in either the first or fifth fingers.

Following plasma exchange (*Fig.* 5), the thumb digital index measured at 21 °C was very similar to that found on the rest of the hand, although at 13 °C the variation noted before treatment still existed. However, there was no significant difference between the mean pressure indices of each of the second, third and fourth fingers at either 13 °C or 21 °C. All the pressure indices had improved after plasma exchange, although they were still less than in the control group.

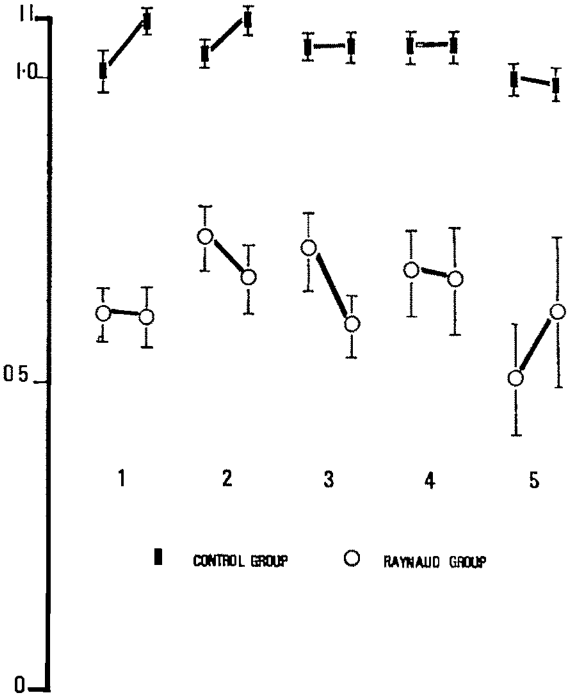

Fig. 2. Variation in digital pressure index at 21 °C in both the control group and the Raynaud group. The ulnar and radial indices of each finger are paired. Each finger is represented by a number. All ulnar values are on the left side of each pair.

At high shear rates ($91\ s^{-1}$) the viscosity levels measured in all 18 patients treated with plasma exchange did not significantly fall over the treatment period. However, both the whole blood viscosity when measured at low shear rate ($0{\cdot}77\ s^{-1}$) and the red cell deformability index (*Fig.* 6) did significantly improve when measured up to 90 days after plasma exchange ($P<0{\cdot}02$). In this group of patients plasma fibrinogen levels were less 90 days after plasma exchange than before, though not significantly so.

After plasma exchange the severe digital ulcers healed in all patients. Three, however, had no symptomatic improvement. Of the 10 patients who were purely symptomatic, 6 said they were better, 1 said she was worse, 2 showed an initial (3-month) improvement and then relapsed. One patient who had improved symptomatically 6 months after treatment felt at the last review (9 months) that his fingers had returned to their pre-treatment condition.

Conclusion

Doppler ultrasound velocimetry is a most useful method of measuring digital artery patency and thus can be considered a suitable means of correlating patients' symptoms with the distribution of patent arteries. Plethysmography can be used to measure either total hand (Peacock, 1960) or digital blood flow and to indicate intraluminal systolic pressure (Nielsen

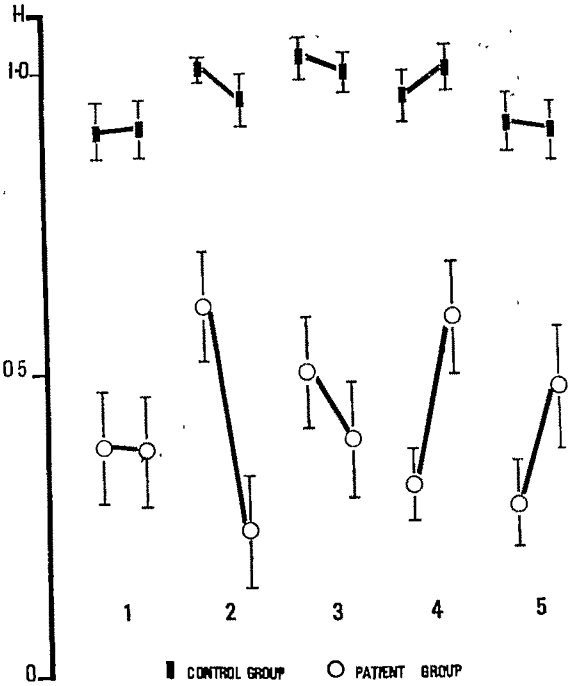

Fig. 3. Variation in digital pressure index at 13 °C in the control group and the Raynaud group. The ulnar and radial indices of each finger are paired. Each finger is represented by a number (1–5). All ulnar values are on the left side of each pair.

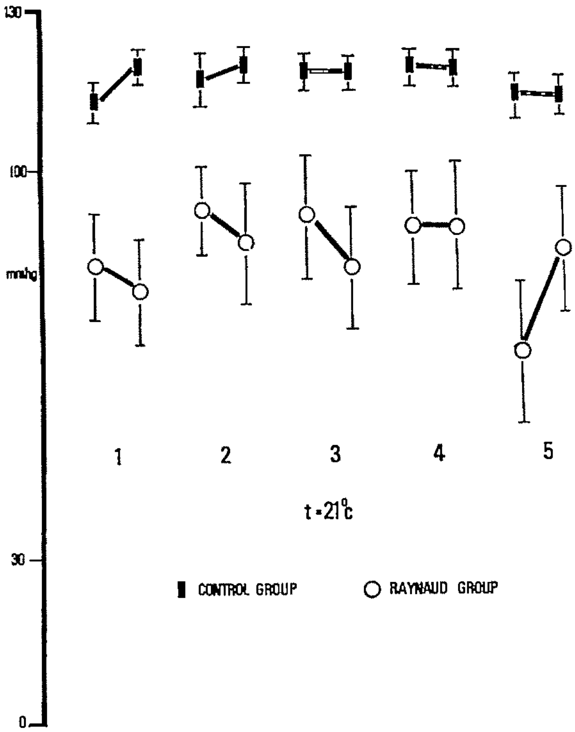

Fig. 4. Digital artery systolic pressures, measured with a Doppler probe and a digital occlusion cuff (T = 21 °C). The ulnar and radial pressures are paired. Each finger is numbered (1–5); ulnar values are on the left side of each pair.

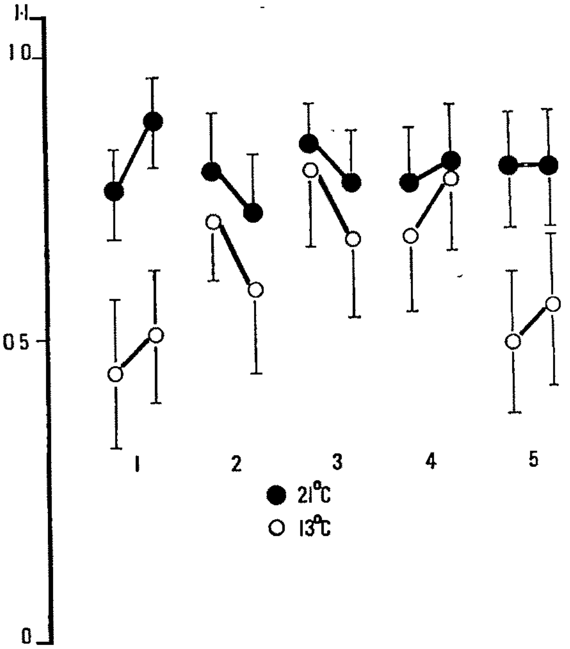

Fig. 5. Digital pressure index after plasma exchange in patients with Raynaud's phenomenon at both 21 °C and 13 °C. The fingers are paired and numbered (1–5). All ulnar values are on the left side of each pair.

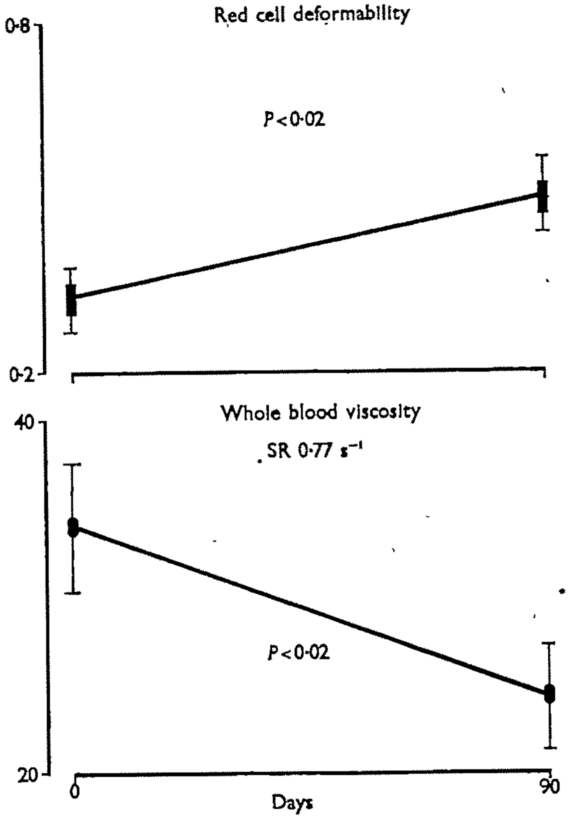

Fig. 6. Changes in red cell deformability and whole blood viscosity in cPoise at 90 days follow-up. Improvement in both values over this period is significant ($P < 0·02$).

and Lassen, 1977). However, Doppler ultrasound techniques are uniquely capable of measuring individual artery pressures rather than total digital pressure (Lassen et al., 1977). It correlates well with arteriographic and thermographic appearances of the digits and thus obviates the need for arteriograms in this relatively benign condition. Furthermore, it can be used quickly to assess digital artery systolic pressures and in our hands has produced values similar to those obtained by others (Nielsen and Lassen, 1977) using plethysmographic techniques.

It was of interest to note that the mean brachial systolic pressure was higher in these patients than in a control group of similar age and sex distribution. This may help confirm the impression that patients with Raynaud's phenomenon do have an increased generalized sympathetic tone (Coffman and Davies, 1975), although it is conceivable that the increased peripheral resistance, caused by the persistent vasospasm in the digital vessels was responsible for this mild hypertension. A vessel remains patent only when the intraluminal systolic pressure is greater than the tone exerted by the muscular walls of the vessel. In the presence of an elevated systemic systolic pressure, only by comparing the digital systolic pressure with the brachial pressure will an accurate estimation of the severity of the disease be obtained as the signs and symptoms in this condition are related to the pressure differential along the arterial segment and not the absolute intraluminal pressure. Our measurements have indicated that the major component of this differential pressure arises in the digital arteries themselves.

Plasma exchange is believed effective in this phenomenon as it may diminish part of the vasospastic component of the phenomenon by removing it from the patient's plasma. We have not yet been able to identify such a component. However, the reports of Gelin (1957) and others have indicated that blood flow in the small vessels and the microcirculation depends mainly on the flow properties of the blood; that is, blood viscosity haematocrit and red cell deformability. It is clear from these data that plasma exchange exerts a profound and long lasting beneficial effect on both the whole blood viscosity and the red cell deformability.

References

COFFMAN J. D. and COHEN A. S. (1971) Total capillary finger tip blood flow in Raynaud's phenomenon. *N. Engl. J. Med.* **285**, 259–263.

COFFMAN J. D. and DAVIES W. T. (1975) Vasospastic diseases—a review. *Prog. Cardiovasc. Dis.* **18**, 123–146.

DOWNS A. R., GASKELL G., MORROW I. et al. (1975) Assessment of arterial obstruction in vessels supplying the fingers by measurement of local blood pressures and skin temperature response test—correlated with angiographic evidence. *Surgery* **77**, 530–539.

GELIN L. E. (1957) Intravascular aggregation and capillary flow. *Acta Chir. Scand.* **113**, 463–465.

HURLOW R. A. and STRACHAN C. J. L. (1978) The clinical scope and potential of isotope angiology. *Br. J. Surg.* **65**, 688–691.

JARRETT P. E. M., MORLAND M. and BROWSE N. L. (1978) Treatment of Raynaud's phenomenon by fibrinolytic enhancement. *Br. Med. J.* **2**, 523.

LASSEN N. A., KRAHENBÜHL B. and HIRAI M. (1977) Occlusion cuff for routine measurement of digital blood pressure and blood flow. *Am. J. Physiol.* **232**, 338–340.

LEWIS T. (1929) Experiments relating to peripheral mechanism involved in spasmodic arrest of circulation in fingers. *Heart* **15**, 7–100.

NIELSEN S. L. and LASSEN N. A. (1977) Measurement of digital blood pressure after local cooling. *J. Appl. Physiol.* **43**, 907–910.

PEACOCK J. H. (1960) The treatment of primary Raynaud's disease of the upper limb. *Lancet* **2**, 65–68.

PINCHING A. J. (1978) Plasma exchange. *Br. J. Hosp. Med.* **10**, 552–558.

PRINGLE R., WALDER D. N. and WEAVER J. P. (1965) Blood viscosity and Raynaud's disease. *Lancet* **1**, 1086.

SCHMID-SCHONBEIN H., RIEGER F. and WURZINGER L. (1975) Rheo-aggregometry: platelet physiology and blood flow. *Proceedings of an International Symposium on Blood Platelets, Istanbul.* Excerpta Medica.

TALPOS G., HORROCKS M., WHITE J. M. et al. (1978) Plasmapheresis in the treatment of Raynaud's disease. *Lancet* **2**, 416–417.

YAO S. T., GOURMOS G., PAPATHANASIOU K. et al. (1972) A method of assessing ischaemia of the hands and fingers. *Surg. Gynecol. Obstet.* **135**, 373–378.

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Simple enucleation and radiotherapy in the treatment of the pleomorphic salivary adenoma of the parotid gland

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SUMMARY

A series of 76 patients with a primary pleomorphic salivary adenoma treated by simple extracapsular enucleation and high energy radiation between 1963 and 1976 is presented. Analysis of the results has shown a very low incidence of complications with only minimal cosmetic deformity. Of the 76 patients, only 5 have been lost to follow-up, 3 patients have died of causes unrelated to the tumour and only 1 patient has developed a recurrence. Further local excision in this patient showed the histological appearances of adenocarcinoma.

THE pleomorphic salivary adenoma is the commonest tumour to occur in the parotid gland, comprising 70–80 per cent of most published series. Because of its slow growth, encapsulation and the rarity of metastases, the tumour is often classified as benign; however, as with many other kinds of neoplasia, 'innocent' and 'malignant' are only relative terms.

Certainly the older surgical methods of treatment, consisting of intracapsular and later extracapsular enucleation alone, resulted in unacceptably high rates of recurrence (McFarland, 1936; Smiddy, 1956). Therefore, wide resection of the tumour by the operation of superficial conservative parotidectomy was advocated (Patey and Thackray, 1958). There is no doubt that after such a procedure the recurrence rate is low, but due to the facial nerve's intimate association with the parotid gland, the identification and preservation of the nerve during the course of the operation is mandatory. The risk of temporary, if not permanent, facial nerve damage during this dissection is quite high (Patey and Moffat, 1961). In 1956, Smiddy observed that when enucleation was followed by interstitial irradiation, no recurrences occurred in the small group of patients so treated. With the development of more sophisticated methods of external irradiation increasing numbers of patients have been treated by simple extracapsular enucleation and irradiation in the Yorkshire region. These patients have recently been studied retrospectively.

Patients and methods

Seventy-six patients with a primary pleomorphic adenoma of the parotid gland have been studied. There were 47 females and 29 males, whose ages ranged at presentation from 12 to 83 years. The distribution of patients in each decade is shown in *Fig.* 1. All the 76 patients complained of a swelling in the region of the parotid gland. The majority did not report to their general practitioner immediately due to the absence of pain and slow growth of the tumour (*Table I*). Only 6 of the 76 patients claimed that a recent increase in size had precipitated presentation. No patient had any facial nerve paresis on presentation. The parotid tumours in this series were more or less evenly distributed between the right and left glands, and no cases of multiple pleomorphic adenoma were seen.

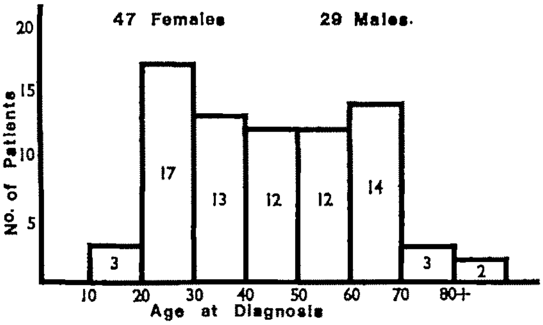

Fig. 1. Age distribution of 76 patients with primary pleomorphic parotid adenomas at time of presentation for treatment.

Table I: DURATION OF TUMOURS AT PRESENTATION

Duration	No. of patients	%
<1 mth	1	1·3
½–1 yr	17	24
1–5 yr	30	42
5–10 yr	19	27
10–20 yr	4	5·6

The majority of the tumours (45 per cent) were situated behind the angle of the jaw; however, others had produced diagnostic confusion by lying behind the ear, in the parotid tail, or high on the cheek. Most of the tumours arose in the superficial parotid tissue and only 2 were of the so-called dumb-bell type, extending through the narrow gap between the ascending ramus of the jaw and the styloid process and stylomandibular ligament to enter the parapharyngeal space. Ninety per cent of the parotid tumours were from 1 to 5 cm in diameter and only a minority were larger. Operative removal of the tumours was carried out through vertical incisions centred directly over the swelling followed by extracapsular enucleation or occasionally with an accompanying cuff of normal salivary tissue, particularly on the superficial surface. Occasionally it was necessary to display the facial nerve at its origin for tumours situated in its immediate vicinity. The wounds were closed in two layers over a soft drain and a firm dressing applied. It was apparent from the operative notes that rupture during dissection had occurred in some 16 of the 76 tumours.

All 76 patients received external irradiation when the skin wound had healed. This was given as supervoltage radiation in the form of cobalt-60 or Mev. linear accelerator radiation using two oblique beams which were modified by wedge filters thus optimizing the dose distribution to the parotid while decreasing the dose to the adjacent normal structures. A bolus was also strapped over the skin of the irradiated area so that the surgical skin incision received adequate irradiation. The patients received approximately 4800 rad, fractioned into fifteen treatments over a 3-week period.

Routine follow-up was carried out for the 5 years following the removal of the tumour. However, recently all 76 patients have been reviewed in the clinic or, if this was not possible, by means of a questionnaire to the patient or his or her general practitioner.

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Results

The parotid surgery was carried out by a variety of surgeons with varying degrees of surgical experience. There were some cases of facial nerve damage but in only 1 patient did this result in permanent disability. In a further 8 patients facial weakness, mainly involving the submandibular division of the facial nerve, was evident postoperatively, resolving spontaneously after a few months. Two patients developed salivary fistulas but these both closed following the radiotherapy. Frey's syndrome, with symptoms of gustatory sweating, was not found in any of the 76 patients. The only complications from the irradiation were some dryness of the mouth and desquamation into the external ear; however, appropriate dental prophylaxis was instigated before the radiotherapy.

The results of the recent follow-up of the 76 patients who had been treated by enucleation and postoperative radiotherapy are shown in *Fig.* 2. Only 5 patients could not be traced and their current status assessed. A further 3 patients have died, all from causes unrelated to their parotid tumours. To our knowledge only 1 patient has developed a recurrent tumour. This 68-year-old female developed a recurrence in the surgical scar 1 year after the initial treatment. This was excised locally but recurred twice more. On the third occasion histology showed adenocarcinoma and total parotidectomy was performed.

Discussion

Seventy-six patients with a primary pleomorphic adenoma of the parotid gland, treated by extracapsular enucleation of the tumour and postoperative radiotherapy between 1963 and 1976, are reported. The patients are comparable with other series (Wyatt et al., 1967; McEvedy and Ross, 1976; Woods et al., 1977) in that the age range was considerably greater than that found in malignant tumours of most other sites and that there was a female predominance. Late presentation for treatment was again a feature.

Enucleation alone results in a high recurrence rate (McFarland, 1936; Stea, 1975), probably due to the presence of residual peripheral nodules of the tumour (Patey and Thackray, 1958). Thus wide resection of this tumour was advised and this continues to be recommended as the treatment of choice (Maynard, 1978). Superficial conservative parotideciomy is, however, a difficult operation, and even when performed by an experienced surgeon, postoperative facial nerve damage is quite common (Patey and Moffat, 1961; Woods et al., 1977). Superficial parotidectomy is complicated by Frey's syndrome in 9–40 per cent of cases (Haws, 1975; Woods et al., 1977).

The recurrence rate following the removal of these tumours is, however, of paramount importance in determining the optimum initial treatment. Recurrences are usually multiple and can often undergo malignant transformation (Wyatt et al., 1967), as did one recurrent tumour in this series. The reported recurrence rates following superficial parotidectomy are low; Woods et al. (1977) reported 8 recurrences out of 360 operations. In our series of 76 patients treated by enucleation and radiotherapy only 1 tumour has recurred. Although long term follow-up in all the patients is not complete, most recurrent pleomorphic tumours occur early, many within 1 year, and nearly all within 5 years (Smiddy, 1956). Certainly the morbidity in this series is lower than would have been expected if superficial parotidectomy had been performed, particularly by general surgeons seeing only a small number of parotid tumours in a year. There have been several other recent reports of the treatment of parotid pleomorphic adenomas by enucleation and radiotherapy. McEvedy and Ross (1976) reported only 2 recurrences out of 73 tumours and Haws (1975) followed up 31 patients with only 1 recurrence. In both series the complications of the initial treatment were minimal and the cosmetic results excellent. It would therefore seem that when modern techniques of irradiation are combined with surgical enucleation the results are comparable with those of the more radical operations of conservative parotidectomy but without its inherent complications.

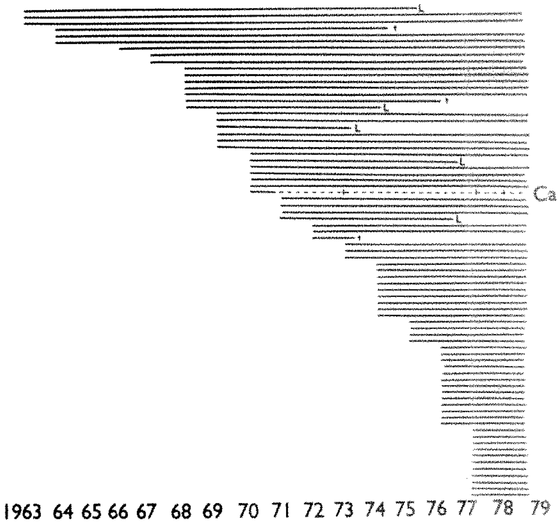

Fig. 2. Results of the follow-up of 76 patients with primary pleomorphic parotid adenomas. (†, Death; L, lost to follow-up.)

Acknowledgements

We thank the consultant surgeons and radiotherapists of the Yorkshire region for permission to review their patients.

References

HAWS C. S. (1975) Pleomorphic adenoma of the parotid gland. *J. R. Coll. Surg. Edinb.* **20**, 25–29.

MCEVEDY B. V. and ROSS W. M. (1976) The treatment of mixed parotid tumour by enucleation and radiotherapy. *Br. J. Surg.* **63**, 341–342.

MCFARLAND J. (1936) Three hundred mixed tumours of the salivary glands, of which sixty-nine recurred. *Surg. Gynecol. Obstet.* **63**, 457–468.

MAYNARD J. (1978) Contemporary surgery: submandibular and parotid gland resection. *Br. J. Hosp. Med.* **20**, 70–78.

PATEY D. H. and MOFFAT W. (1961) A clinical and experimental study of functional paralysis of the facial nerve following conservative parotidectomy. *Br. J. Surg.* **48**, 435–440.

PATEY D. H. and THACKRAY A. C. (1958) The treatment of parotid tumours in the light of a pathological study of parotidectomy material. *Br. J. Surg.* **45**, 477–487.

SMIDDY F. G. (1956) Treatment of mixed parotid tumours. *Br. Med. J.* **1**, 322–325.

STEA G. (1975) Conservative surgical treatment of mixed parotid tumours of the parotid gland. *J. Maxillofac. Surg.* **3**, 135–137.

WOODS J. E., WEILAND L. H., CHONG G. C. et al. (1977) Pathology and surgery of primary tumours of the parotid. *Surg. Clin. North Am.* **57**, 565–573.

WYATT A. P., HENRY L. and CURWEN M. P. (1967) Salivary tumours. *Br. J. Surg.* **54**, 636–645.

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Segmental air plethysmography during arterial reconstruction

R. N. BAIRD, P. W. DAVIES AND D. R. BIRD*

SUMMARY

Sixty-one patients undergoing 83 lower limb reconstructions for chronic arterial ischaemia or aortic aneurysm from April 1977 to March 1979 were monitored intraoperatively using the pulse volume recorder (PVR), Doppler auscultation and palpation of pedal pulses. Nine technical defects (11 per cent) were recognized 5 min after declamping and corrected before the operative wound was closed. In 31 grafts to the popliteal artery median ankle PVR amplitude increased from 4·5 mm (95 per cent confidence limits, 2–6 mm) at the start of the operation to 18 mm (14–21 mm, $P<0{\cdot}0001$ *Wilcoxon). Four poor PVR wave forms were successfully improved by operative revision. Initial median calf PVR amplitude with isolated aortic or iliac artery occlusions in 30 limbs was 41 mm (29–56 mm), similar to that in 22 control limbs (38 mm, 28–53 mm), and did not alter following successful reconstruction. In this group there were 2 operative revisions and all grafts were patent postoperatively.*

*In successful proximal reconstructions of 22 severely ischaemic limbs with combined proximal and distal disease, median PVR amplitude fell from 10·5 mm (6·5–14 mm) to 8 mm (6·5–15 mm, not significant). There were 3 operative revisions and all grafts remained patent postoperatively. In this group with combined proximal and distal disease pulse wave transit time (*R *wave of ECG to peak calf PVR wave form) became shortened from 577 ms (542–633 ms) to 481 ms (467–495 ms,* $P<0{\cdot}05$*). Where operative correction was required, transit time on initial declamping became prolonged but fell to less than the pre-reconstruction transit time following successful revision. These results suggest that the information provided by intraoperative monitoring with the PVR will contribute towards a reduction in early graft occlusions and re-explorations in the postoperative period.*

Table I: OPERATIVE REVISIONS OF TECHNICAL FAULTS DETECTED BY VARIOUS MONITORING TECHNIQUES

Monitoring technique	Faults detected and corrected	%
Arteriography		
Renwick et al. (1968)	15/55	27
Taylor (1978)	19/126	15
Strain gauge plethysmography		
Dickson et al. (1965)	19/55	34
Pulse volume recorder		
O'Donnell et al. (1978)	4/59	7
Present series	9/83	11

Table II: ARTERIAL RECONSTRUCTIONS OF 83 LIMBS IN 61 PATIENTS

Proximal grafts	
(52 limbs in 33 patients)	
Aorto-iliac/femoral	31
Aneurysm—sleeve graft	14
Transpubic	3
Axillobifemoral	4
Grafts to the popliteal artery	
(31 limbs in 28 patients)	
Femoropopliteal vein	18
Iliopopliteal dacron	13
Control limbs	22

THE pulse volume recorder (PVR)† is a new development in segmental plethysmography of the limbs in which a signal corresponding to the arterial pressure pulse is obtained non-invasively from an air-filled sphygmomanometer cuff (Raines et al., 1976; Baird and Davies, 1977). During the past year, preliminary reports have appeared describing the use of the PVR to monitor intraoperatively arterial grafting procedures (Bird et al., 1978; O'Donnell et al., 1978).

The pulse volume is monitored intraoperatively so that technical defects can be identified and corrected before the operative wound is closed. Failure to detect a substandard reconstruction at this time will result in early graft occlusion and expose the patient to the hazards of a re-exploration. Secondary operations have a high morbidity and mortality and the prognosis for graft patency is poor even with an early and apparently successful re-exploration (Craver et al., 1973).

Monitoring techniques were developed to combat early graft failures which, for femoropopliteal operations, range from 6 to 21 per cent (Renwick et al., 1968; Keitzer et al., 1972; Craver et al., 1973; Myhre, 1977). The results of proximal grafts to the iliac and femoral arteries are better, but in one series symptoms were not improved in 11 per cent, and some patients became substantially worse (Garrett et al., 1977). Following the introduction of routine intraoperative arteriography (Renwick et al., 1968; Taylor, 1978), electromagnetic flowmetering (Terry et al, 1972; Roberts and Cotton, 1977), use of a sterile Doppler ultrasound probe (Keitzer et al., 1972) and strain gauge plethysmography (Dickson et al., 1965), technical defects were detected in 15–34 per cent of arterial operations *at the time* so that corrections could be made before the reconstruction was completed (*Table I*). The results of reconstruction are related to the degree of preoperative ischaemia, but since the clinical indications for operations vary from one series to another, these results are not strictly comparable with one another. The proportion of limbs revascularized for rest pain or gangrene ranged from 18 per cent (Garrett et al., 1977) to 50 per cent (present series) and some authors (O'Donnell et al., 1978) excluded limbs in which Doppler pedal pulses were absent preoperatively.

Since our preliminary results with the PVR were encouraging, we embarked on a prospective trial of intraoperative monitoring, in which PVR amplitude and transit time were compared with Doppler transit time, the return of palpable or Doppler-audible foot pulses and the clinical outcome of operation.

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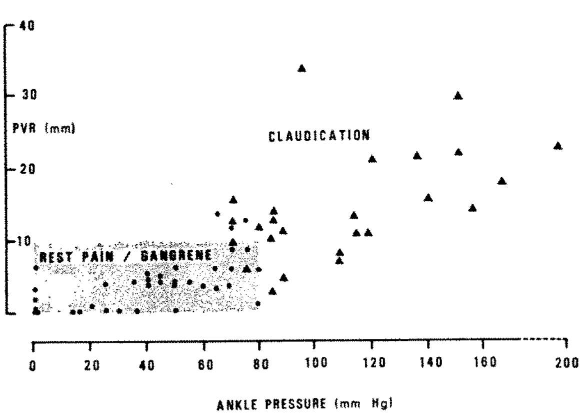

Fig. 1. Ankle PVR amplitude plotted against ankle systolic pressure. Note the separation of rest pain/gangrene from claudication at an ankle PVR of 10 mm and ankle pressure of 80 mmHg.

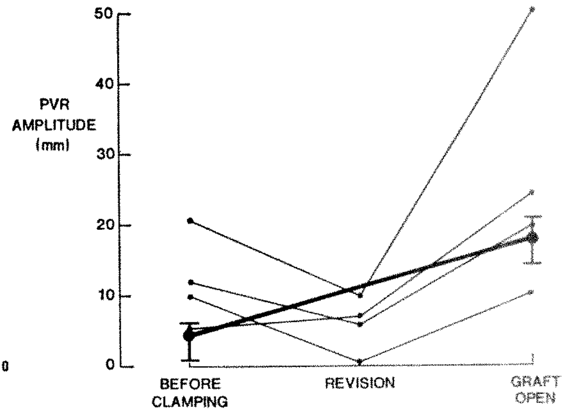

Fig. 2. PVR amplitudes in grafts to the popliteal artery ($n = 31$). Note the low initial amplitude and striking improvement in amplitude following successful arterial grafts.

Table III: CLINICAL DIAGNOSIS OF ARTERIAL RECONSTRUCTIONS

Limbs reconstructed	Rest pain/ gangrene	Claudication	Aneurysm
Grafts to popliteal artery (31)	24	7	—
Proximal grafts			
SFA occluded (22)	17	5	—
SFA patent (30)	1	13	16
Total	42	25	16

SFA, Superficial femoral artery.

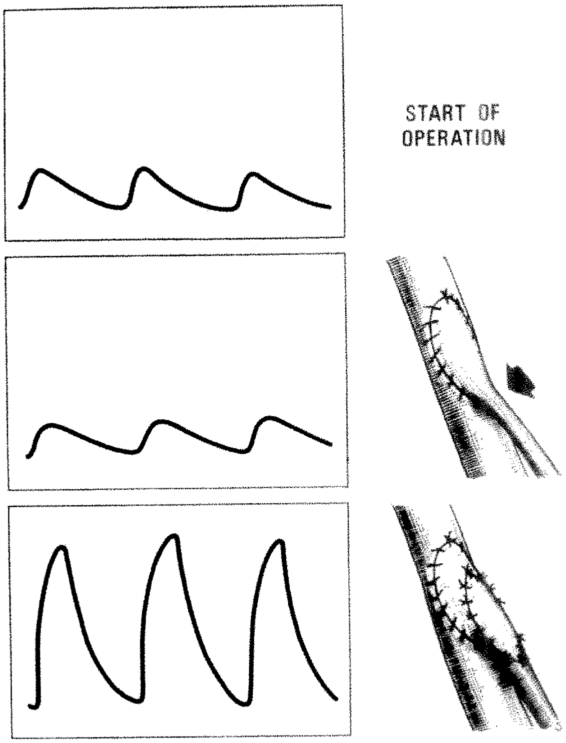

Fig. 3. PVR wave forms from a femoropopliteal vein graft with a stenosis at the proximal anastomosis (arrow). Note the markedly increased PVR wave form amplitude following insertion of a vein patch gusset.

Patients and methods

Of 147 patients who were monitored during arterial operations at Bristol Royal Infirmary in the 2-year period from April 1977 to March 1979, 61 (mean age 59 years) were studied who underwent reconstructions of 83 lower limbs for chronic ischaemia or aortic aneurysm (*Table II*). Operations for acute arterial ischaemia and reconstructions of the upper limb, carotid and renal arteries were excluded. Diabetes or abnormal glucose tolerance was noted in 9 per cent.

Lower limb ischaemia was evaluated clinically, by segmental limb PVR and Doppler systolic pressure measurements at the thigh, calf and ankle, and by arteriography. In all but 3 cases rest pain or gangrene was associated with an ankle pressure of less than 80 mmHg together with an ankle PVR amplitude of less than 10 mm (*Fig.* 1). More than three-quarters of proximal reconstructions in the presence of an occluded superficial femoral artery and of grafts to the popliteal artery were for ischaemic rest pain or gangrene. Proximal bypass of an isolated aortic or iliac artery occlusion was the most common operation for intermittent claudication (*Table III*).

Monitoring sphygmomanometer cuffs were applied to the calves for proximal grafts and to the ankles for grafts to the popliteal artery. The cuffs were applied firmly so that inflation with 75±10 ml of air resulted in a pressure in the cuff of 65 mmHg. A Perspex hood was placed over the feet to enable sequential Doppler auscultation and palpation of pedal pulses once sterile drapes had been applied. Recordings were made as follows: after establishment of stable anaesthesia; after mobilization of the arteries before clamping; 5 min after declamping; 30 min after declamping; 5 h later in the recovery room.

The output from the PVR was displayed on a strip chart recorder and, in addition, the wave forms were displayed for the surgeon on a storage oscilloscope. PVR, Doppler and ECG were recorded on FM cassette tape. PVR amplitude (mm) was measured from three consecutive wave forms, as was upstroke time (ms), defined as the time interval between the foot of the upstroke and the point of maximum deflection (Bird et al., 1978). Transit time was calculated from the R wave of the ECG to the peaks of the PVR and Doppler wave forms (Harper et al., 1974).

Since the distribution of data in most groups was heavily skewed all results are given as median values and 95 per cent confidence limits.

Statistical analyses were by the Wilcoxon matched pairs signed ranks test.

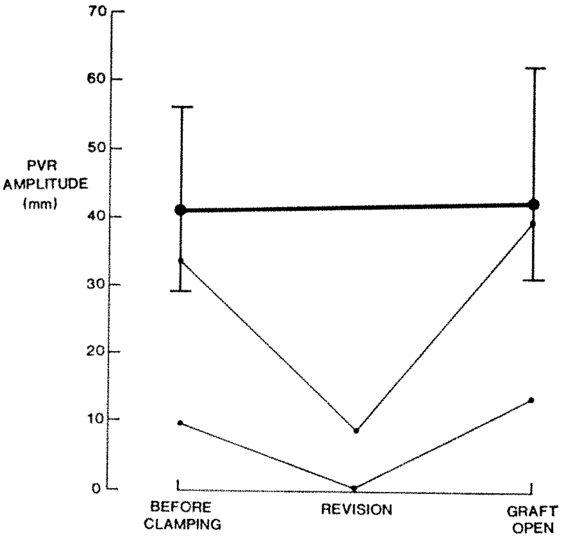

Fig. 4. PVR amplitudes in proximal reconstructions with a patent superficial femoral artery. Note the absence of resting ischaemia initially and the lack of change after declamping. In 2 cases a marked fall in amplitude occurred and operative revision was necessary.

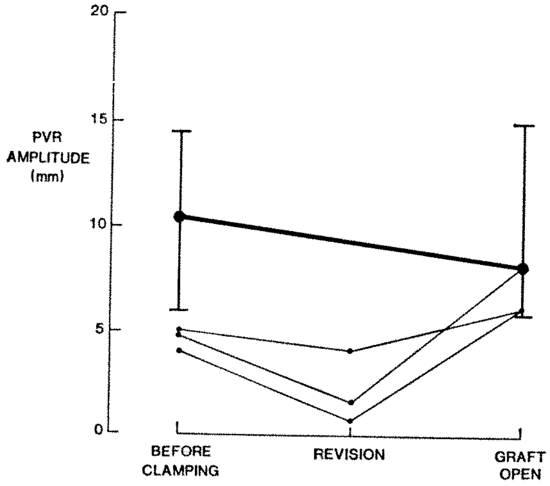

Fig. 5. PVR amplitudes in proximal reconstructions with an occluded superficial femoral artery. The initial amplitude is very low and does not increase immediately after successful reconstruction.

Results

Results were grouped as follows: grafts to the popliteal artery; proximal grafts for isolated aortic or iliac artery occlusions; and proximal grafts in the presence of an occluded superficial femoral artery. Control limbs were also studied.

Grafts to the popliteal artery (n = *31*)

Pulse volume recordings (*Fig.* 2): The initial median ankle PVR amplitude was low at 4·5 mm (2–6 mm), and in successful grafts there was a fourfold increase in PVR amplitude to 18 mm (14–21 mm, $P<0.0001$). A poor initial result shown by decreased PVR amplitude in 4 vein grafts was improved by insertion of a vein gusset at the proximal anastomosis (*Fig.* 3). One vein graft was attached to a previously inserted aortofemoral Dacron graft, and balloon catheter embolectomy was required to remove fragments of intima from the Dacron/vein anastomosis. All revised grafts subsequently remained patent.

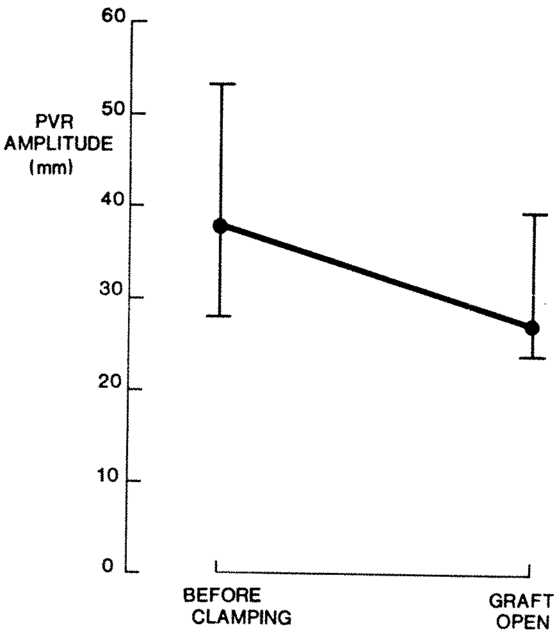

Fig. 6. Calf PVR amplitude changes in 22 control limbs. Recordings were made at the same stages as for the operated limbs. Note the fall in amplitude.

Pedal pulses: Preoperatively a Doppler pedal pulse was heard in all but one of the limbs but a pedal pulse was palpable in only one limb. At the end of operation Doppler pulses were invariably present but a palpable pulse was present in only one-quarter of the vein grafts studied.

Outcome: Two vein graft failures within the first 5 days were due to use of a vein of inadequate size (<4 mm diameter). Heparin (for DVT) induced anastomotic haemorrhage necessitating reoperation in 3 limbs, which in turn resulted in thrombosis of 2 vein grafts. Fourteen of 18 vein grafts (78 per cent) were patent at discharge from hospital.

Grafts to the iliac, common femoral and profunda arteries

Superficial femoral artery patent (n = *30*): The initial PVR amplitude was normal (41 mm, 29–56 mm) and following a successful reconstruction, a similar value (42 mm, 31–62 mm) was obtained (*Fig.* 4). Two operative revisions (balloon catheter embolectomy and graft extension from the iliac to the femoral artery) were required because the initial post-reconstruction wave form disappeared in one instance and was severely damped in the other, amplitude falling to only 24 per cent of the pre-reconstruction value (from 34 mm to 8 mm). All grafts remained patent postoperatively, with early return of pedal pulses.

Superficial femoral artery occluded (n = *22*): These limbs were severely ischaemic preoperatively with a

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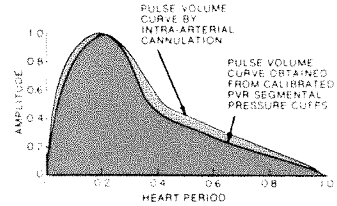
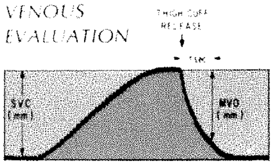


Comparison of pressure contours obtained with the PVR and direct cannulation of the common femoral artery.



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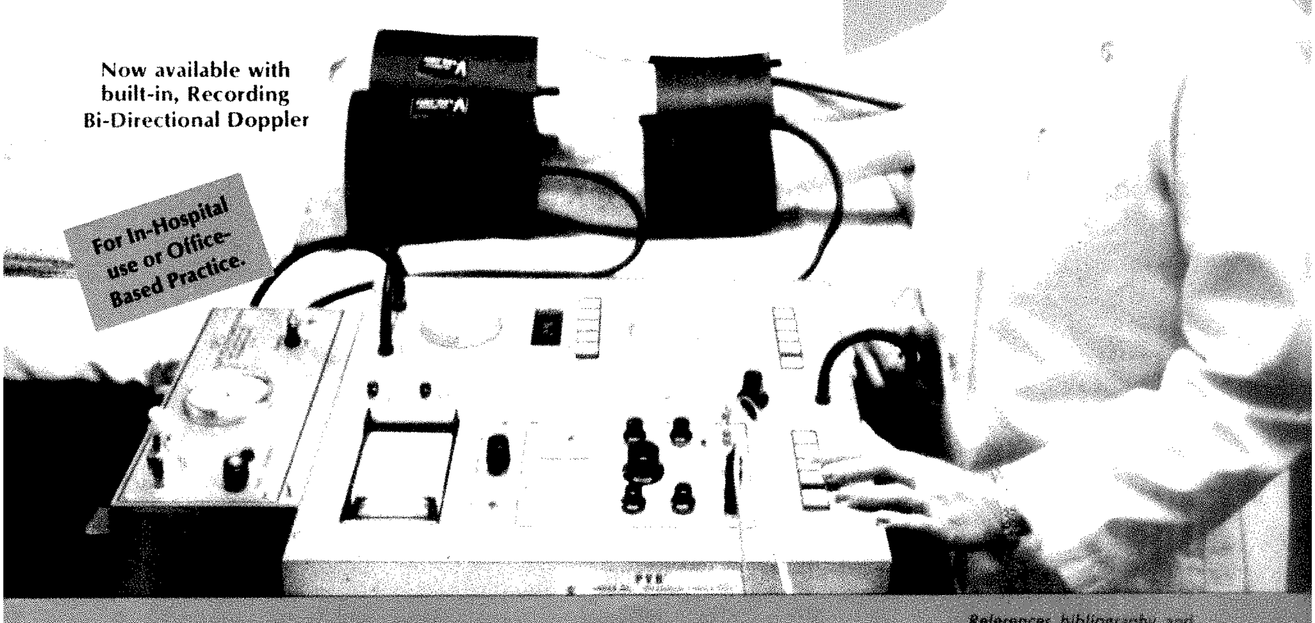

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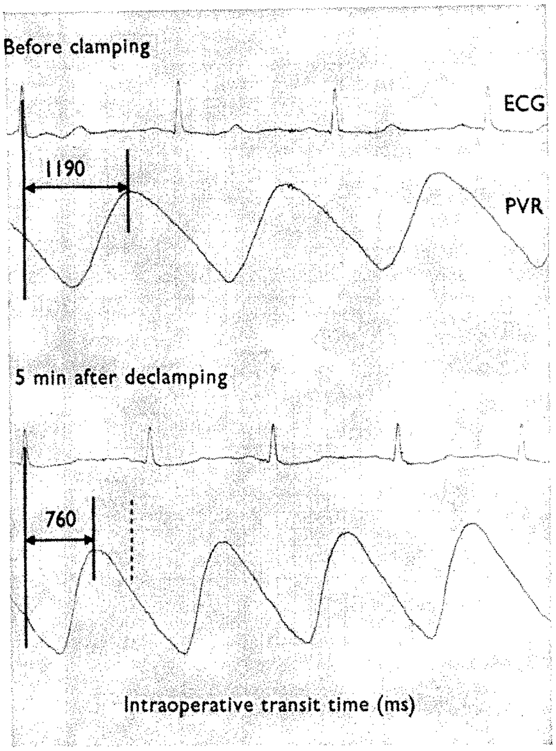

Fig. 7. Following successful proximal reconstruction of an occluded iliac artery, transit time from the R wave of the ECG to peak calf PVR wave form was reduced from 1190 ms to 760 ms. Note the absence of change in PVR amplitude.

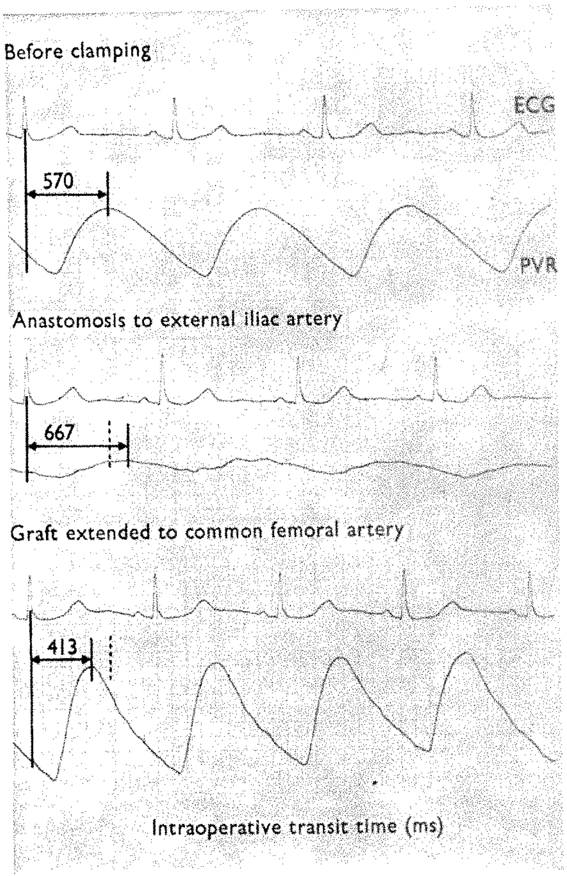

Fig. 8. A poor initial result (centre) after aorta-to-external-iliac reconstruction. Note that the transit time became reduced to less than the initial value after successful revision to the common femoral artery (bottom).

low initial calf PVR amplitude of 10·5 mm (6·5–14 mm) which was insignificantly altered to 8 mm (6·5–15 mm) after a successful reconstruction (*Fig.* 5).

In 3 cases deterioration in the initial post-reconstruction wave form prompted operative revision (balloon catheter embolectomy in 2, graft extended from iliac to femoral artery in 1). This deterioration was detected in 2 cases by an increase in transit time. No pedal pulses were palpable in any limb at any stage and ankle Doppler signals were absent in 23 per cent and indecipherable in a further 18 per cent. All grafts remained patent postoperatively.

Control limbs (n = *22*)
PVR wave form amplitude fell from 38 mm (28–53) to 27 mm (23–39 mm, $P<0{\cdot}02$) during the reconstruction (*Fig.* 6), but amplitude was restored to normal in the recovery room. The controls were contralateral limbs during femoropopliteal reconstructions and lower limbs during subclavian and axillary artery reconstructions.

Effect of arterial dissection: Mobilization of the arteries at the sites of proximal and distal anastomoses occasionally resulted in a reduction in PVR amplitude greater than that observed simultaneously in control contralateral limbs, although in all three groups of patients PVR amplitude before and after arterial dissection was not significantly different. The most marked changes were seen after aorto-iliac dissection in patients with rest pain or gangrene, and in 4 limbs in this group the PVR wave form was completely lost after dissection along with pedal Doppler signals. These changes were not associated with a reduction in the brachial systolic pressure.

Transit time: In limbs with combined proximal and distal occlusions, transit time was initially prolonged at 577 ms (542–633 ms) compared with limbs with patent distal systems at 455 ms (430–503 ms) or with Harper's age-matched control subjects (403 ms) (Harper et al., 1974).

In 23 proximal reconstructions where the distal arteries were patent, transit time fell to near normal values, and an illustrative example is given in *Fig.* 7. Ankle Doppler velocity/time wave forms were always present at the start of operation and Doppler transit time correlated well with PVR transit time ($r = 0{\cdot}96$).

Following successful proximal reconstruction in the presence of distal disease, transit time at 5 min after declamping was significantly shortened (481 ms, 467–495 ms, $P<0{\cdot}05$). In two instances where a revision was necessary, transit time was prolonged on initial declamping (from 570 to 667 ms and from 493 to 607 ms) and was only reduced to less than the pre-reconstruction value after operative corrections were made (*Fig.* 8). In this group calf PVR wave form was used to calculate the transit time because in only

4 of 7 limbs could a usable Doppler signal be detected at 5 min after declamping.

In separate studies of patients under general anaesthesia, the effects of alterations of heart rate and systemic blood pressure on transit time were measured. The heart rate was increased from 65 beats per minute to 110 beats per minute by administration of graded increments of atropine and isoprenaline. The transit time responded by becoming steadily shortened at the rate of 1·5 ms per unit increase in heart rate. Introduction of this correction factor did not affect the significance of the examples illustrated or the overall results. Transit time was not affected by fluctuations of brachial systolic pressure in the range of 85–135 mmHg.

Discussion

A prompt and substantial increase in PVR amplitude at 5 min after declamping a graft to the popliteal artery allowed the wound to be closed without delay and with confidence that a successful result had been obtained. The PVR signal was equally satisfactory for both femoropopliteal and iliopopliteal grafts. If, when the PVR was repeated at 30 min, there was confirmation of a good technical result, the probability of graft patency was high. Detection of palpable pulses in only 25 per cent of grafts suggests that pulse palpation at this vital stage is an unreliable method of assessment. Inspection of the feet was also found to be an insensitive method since more than half the patients with successful grafts did not lose the coldness and pallor of the ischaemic foot until in the recovery room or later.

Measuring lower leg perfusion immediately after a proximal reconstruction in the presence of an occluded outflow tract is perhaps the greatest test of a monitoring system; in this group of technically demanding reconstructions for severely ischaemic limbs the preliminary results of PVR transit time measurements are most encouraging. It should not be forgotten that a functionally inadequate graft in a heparinized patient may pulsate vigorously, only to thrombose a few hours later.

In this group PVR amplitude at 5 min is not a reliable indicator of an effective reconstruction, although graft revision was necessary if PVR amplitude upon declamping was less than 38 per cent of the initial value. These results confirm earlier reports (Raines et al., 1976; O'Donnell et al., 1978).

Although PVR amplitude may be unhelpful in this group, PVR upstroke time is significantly reduced in successful grafts and is reliably associated with postoperative patency (Bird et al., 1978). This increased wave form pulsatility is also manifest as a reduction in transit time, which has been measured in young and old normal subjects (Harper et al., 1974) and in the diagnosis of arterial occlusive disease (Craxford and Chamberlain, 1977) but not hitherto for intraoperative monitoring,

A useful feature of the PVR monitoring technique is its simplicity and ease of interpretation. Increased amplitude in grafts to the popliteal artery or shortened transit time in proximal grafts is associated with a successful clinical outcome. If the anticipated PVR improvement is not present at 5 min after declamping, effective remedial action can be taken without delay. The success of any operative revision can be readily confirmed. The recordings are stable and can be made by a nurse in the operating theatre or recovery room.

Our results suggest that the PVR is a significant advance in intraoperative monitoring and that the information it provides will contribute towards a reduction in graft occlusions and re-explorations in the early postoperative period.

Acknowledgements

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References

BAIRD R. N. and DAVIES P. W. (1977) Evaluation of a pulse volume recorder as a method of assessing peripheral vascular disease. *Br. J. Surg.* **64**, 825.

BIRD D. R., DAVIES P. W. and BAIRD R. N. (1978) Intraoperative monitoring of profunda revascularization using a pulse volume recorder. *Br. J. Surg.* **65**, 825–826.

CRAVER J. M., OTTINGER L. W., DARLING R. C. et al. (1973) Haemorrhage and thrombosis as early complications of femoropopliteal bypass grafts. Causes, treatment and prognostic significance. *Surgery* **74**, 839–845.

CRAXFORD A. D. and CHAMBERLAIN J. (1977) Pulse wave form transit ratios in the assessment of peripheral vascular disease. *Br. J. Surg.* **64**, 449–452.

DICKSON A. H., STRANDNESS D. E. and BELL J. W. (1965) The detection and sequelae of operative accidents complicating reconstructive arterial surgery. *Am. J. Surg.* **109**, 143–147.

GARRETT W. V., SLAYMAKER E. E., HEINTZ S. E. et al. (1977) Intraoperative prediction of symptomatic result of aortofemoral bypass from changes in ankle pressure index. *Surgery* **82**, 504–509.

HARPER D. R., KELMAN G. R., MAVOR G. E. et al. (1974) Time interval between ECG R wave and peak flow velocity in leg arteries of normal humans. *J. Physiol.* (*Lond.*) **239**, Proceedings, pp. 21–22.

KEITZER W. F., LICHTI E. L., BROSSART F. A. et al. (1972) Use of the Doppler ultrasonic flowmeter during arterial vascular surgery. *Arch. Surg.* **105**, 308–312.

MYHRE H. O. (1977) Local complications following surgical treatment of lower limb atherosclerosis. *Acta Chir. Scand.* **143**, 27–32.

O'DONNELL T. F., CROSSMAN D. and CALLOW A. D. (1978) Non-invasive intraoperative monitoring: a prospective study comparing Doppler systolic occlusion pressure and segmental plethysmography. *Am. J. Surg.* **135**, 539–546.

RAINES J. K., DARLING R. C., BUTH J. et al. (1976) Vascular laboratory criteria for the management of peripheral vascular disease of the lower extremities. *Surgery* **79**, 21–29.

RENWICK J., ROYLE J. P. and MARTIN P. (1968) Operative angiography after femoropopliteal reconstruction—its influence on early failure rate. *Br. J. Surg.* **55**, 134–136.

ROBERTS V. C. and COTTON L. T. (1977) Electromagnetic blood flow measurements during extended deep femoral angioplasty. *Acta Chir. Scand.* **143**, 413–416.

TAYLOR R. S. (1978) Peroperative arteriography in lower limb revascularization procedures. In: Proceedings of the 27th International Congress of the European Society of Cardiovascular Surgery. *Documentation Médicale Oberval* pp. 105–107.

TERRY H. J., ALLAN J. S. and TAYLOR G. W. (1972) The relationship between blood-flow and failure of femoropopliteal reconstructive arterial surgery. *Br. J. Surg.* **59**, 549–551.

Br. J. Surg. Vol. 66 (1979) 723–726

Long term results of autogenous vein bypass grafts in femoropopliteal arterial occlusion

R. P. GRIMLEY, M. L. OBEID, F. ASHTON AND G. SLANEY*

SUMMARY

The results of 329 consecutive autogenous vein grafts carried out between January 1962 and June 1973 have been reviewed. The 5- and 10-year mortality rates were 14·6 per cent and 18·7 per cent respectively.

The corresponding patency rates were 70 per cent at 5 years and 34 per cent at 10 years, the lowest patency (27·8 per cent) occurring in below-knee anastomoses with grafts of 5 mm or less in diameter. As others have noted, the state of the popliteal–tibial run-off vessels had a considerable influence on long term patency rates. In severely ischaemic limbs, the limb salvage rate following this operation was 77 per cent.

An analysis of symptoms, associated disease and complications is presented and discussed.

No valid conclusions could be made regarding the effect of lumbar sympathectomy and postoperative anticoagulants on long term patency.

This review has confirmed the findings of earlier studies that a satisfactory 5-year patency rate and a gratifying limb salvage rate can be achieved with an extremely low operative mortality rate of 0·37 per cent. Despite the presence of widespread atherosclerotic arterial disease, the 5-year mortality rate is 14·6 per cent, indicating that an attempt at reconstructive surgery is usually well worth while.

THE 5-year results following femoropopliteal venous bypass grafts were reported from this unit in 1970 (Baddeley et al., 1970). Since results utilizing alternative graft prostheses are being reported we considered it worth while to review our own series in which some patients have now reached 12-year follow-up.

Patients and methods

From January 1962 to June 1973, 329 autogenous vein grafts were implanted in 272 patients, of whom 22 were women. Symptoms were bilateral in 138 patients, of whom 57 required bilateral surgery (18 per cent of the total number). Twenty-one patients were lost to follow-up; a further 26 patients had left the area but adequate data were obtained from their general practitioners.

The influence of age on graft failure is summarized in *Table I*. Most patients were aged 50–69 years and the largest number of graft failures—61·3 per cent—was observed in the 40–49 age group. The overall mean failure rate in the under-50 age group (47·5 per cent) was slightly higher than in the over-50 age group (40·6 per cent), but there are obvious differences in the number of operations performed.

Presenting symptoms were disabling intermittent claudication in 264 limbs, rest pain was present in 65 limbs and 21 limbs had trophic changes; both rest pain and trophic changes were present in 37 limbs. An analysis of type and duration of symptoms is presented in *Table II*. Four patients with superficial femoral artery trauma and 11 with distal limb aneurysms are also included.

In patients with signs of advanced ischaemia and intermittent claudication of more than 2 years' duration, the trophic changes were relatively recent events precipitating surgical referral. In 124 limbs symptoms had been present for 1 year or longer; the remaining 168 had shorter histories necessitating earlier operation because of advanced ischaemia.

Table I: AGE DISTRIBUTION

Age (yr)	No. of limbs	Eventual graft failure No.	Eventual graft failure %
Under 40	15	5	33·3
40–49	44	27	61·3
50–59	112	50	44·6
60–69	138	55	39·8
70–77	18	5	27·8
80–89	2	1	50·0

Table II: DURATION AND TYPE OF SYMPTOM

Type of symptom	Duration <6 mth	6–12 mth	1–2 yr	2–3 yr	>3 yr	Total
IC	27	42	39	16	20	141
RP	4	2	—	—	—	6
T	1	1	1	—	—	3
Other	7	1	—	1	1	10
T+other	1	—	1	—	—	2
IC+RP	18	18	18	2	9	65
IC+T	6	8	5	1	1	21
RP+T	3	2	—	1	1	7
IC+RP+T	12	12	5	4	4	37

IC, Intermittent claudication; RP, rest pain; T, trophic change (including 3 patients with frank gangrene); other symptoms relate to superficial femoral artery trauma and limb aneurysms.

Of the 141 claudicants, 121 had had symptoms for more than 6 months and 118 had a measured walking distance on a flat hospital corridor of 200 yards (185 m) or less. The majority of the patients were operated upon before routine Doppler assessment became available.

Arteriography, electrocardiography, biochemical and haematological profiles were performed routinely. Dyspepsia was investigated because of the potential problems associated with anticoagulation and to exclude malignancy.

At annual follow-up grafts were designated patent if the graft or pedal pulses were palpable; a few were investigated by further angiography because of subsequent symptoms in the contralateral limb or proximal aorto-iliac disease. In the majority of cases symptoms and signs of ischaemia were relieved. In 8 patients with a patent graft ischaemia progressed owing to progressive occlusive atherosclerotic disease in the run-off vessels.

Results

Of the 329 grafts, 134 occluded during a follow-up period of 6 months to 13 years, mean follow-up being 6·53 years.

Mortality

Of 272 patients, 60 (22 per cent) died from causes shown in *Table III*. Only 1 patient died postoperatively—an operative mortality of 0·37 per cent. The late mortality at 2 years, 5 years and 10 years was 5·1, 14·6 and 18·7 per cent respectively.

In the deceased patients 34 grafts were patent and 31 occluded, so that the percentage of grafts functioning at the time of death was 52.

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Graft patency

The percentage patency was calculated from survivors alone. Thus 137 grafts were followed up for 5 years or more and of these 96 were patent—a 5-year patency of 70·08 per cent. In *Table IV* it can be seen that patency falls markedly from 69·51 per cent to 34·48 per cent after 7 years' follow-up.

Arteriograms were available for review in 297 of the patients with atherosclerosis. In 134 less than 15 cm of the femoropopliteal segment was occluded and in 163 cases more extensive occlusions were present, graft patency being 67·9 per cent and 63·8 per cent respectively. These similar patency rates indicate that the graft is an efficient bypass around the diseased segment. The alternative surgical technique, thromboendarterectomy, is inadequate in this respect, as we have already emphasized in our earlier reports (Baddeley et al., 1968).

Table III: CAUSES OF DEATH

Cause of death	No. patients	Total grafts	Occluded grafts	Patent grafts
Cerebrovascular accident	14	15	9	6
Myocardial infarction	27	30	17	13
Congestive heart failure	4	4	1	3
Cancer	11	12	4	8
Respiratory failure	3	3	0	3
Cirrhosis	1	1	0	1
Totals	60	65	31	34

Table IV: FINAL PATENCY RATE

Duration of follow-up	Total grafts	Deaths	Total grafts followed up	Patent grafts No.	%
Postoperative	320	1	319	298	93·41
6 mth	317	1	316	295	93·66
1 yr	311	4	307	281	91·54
2 yr	284	11	273	248	90·81
3 yr	242	5	237	201	84·8
4 yr	203	17	186	152	81·19
5 yr	145	8	137	96	70·08
6–7 yr	111	6	105	73	69·51
8–10 yr	65	7	58	20	34·48
>10 yr	27	5	22	7	31·83

Patency related to popliteal–tibial run-off

In a previous report, run-off was graded as follows: 'excellent' with normal popliteal and tibial vessels; 'good' when minimal disease of the popliteal and tibial arteries was present; 'moderate' with 'scalloping' of the popliteal artery and occlusion of one of the three main calf arteries or narrowing of the others; 'poor' when two or all three calf arteries were occluded (Baddeley et al., 1970).

The patency rates, summarized in *Table V*, for good and moderate run-off were satisfactory, with 5-year patency rates of 75 per cent. Patency declined after this time, however, especially where run-off was only moderate, with a resultant 10-year patency rate of 10 per cent. Initial patency rates in the poor run-off group were comparable to the 5-year rates in the better groups, but 5 years postoperatively only 50 per cent of grafts remained patent and all of these had occluded by the eighth postoperative year. Of the 22 patients whose grafts occluded in this group only 9 required a major amputation.

Patency, site of distal anastomosis and graft diameter

The minimal diameter of 312 implanted grafts was noted at operation. The outcome of these grafts is summarized in *Table VI* with a mean follow-up of 6·53 years.

The diameter of the graft was greater than 5 mm in 271 cases, but it is evident that above-knee grafts are associated with higher patency regardless of diameter. Grafts inserted at the level of the knee joint have satisfactory patency values where the calibre is greater than 5 mm.

Very poor results were found in vein grafts of small calibre inserted below the knee joint. Since poor run-off could influence the poor results of below-knee grafts, run-off studies were correlated with the site of distal anastomosis (*Table VII*).

Patency rates with below-knee anastomoses are lower than with above-knee anastomoses whatever the degree of atherosclerosis in the run-off vessels. Our series firmly supports the view that below-knee grafts of small calibre inserted into limbs with poor run-off usually fail.

Table V: DURATION OF FOLLOW-UP AND GRAFT PATENCY IN PATIENTS WITH GOOD, MODERATE AND POOR POPLITEAL TIBIAL RUN-OFF

	Good			Moderate			Poor		
		Patency			Patency			Patency	
Duration	Grafts	No.	%	Grafts	No.	%	Grafts	No.	%
1 mth	109	101	92·6	75	71	95·96	48	35	76·08
6 mth	108	94	87·0	72	59	84·30	46	26	57·78
1 yr	95	80	84·2	62	49	83·03	43	24	57·15
2 yr	86	65	79·3	53	38	79·17	39	20	57·14
3 yr	68	52	78·8	39	27	77·13	30	15	55·55
4 yr	57	40	76·9	27	18	75·00	22	11	55·00
5 yr	42	32	76·9	21	14	73·67	14	7	50·00
6–7 yr	34	25	75·8	13	7	70·00	11	3	27·26
8–10 yr									
8 yr	14	9		2	2		1		
9 yr	6 }25	3 }15	71·4	2 }6	—	60·00	2 }6	0	0
10 yr	5	3		2	1		3		
11 yr	7 }15	4 }9		1	—	50·00	2 }3	0	0
12 yr	8	5	69·2	1 }2	1		1		

NB, Patency rate is calculated from survivors alone.

Limb salvage

Advanced ischaemia (pain, trophic changes, including ulceration or gangrene) indicating immediate amputation was present in 185 legs. The autogenous vein grafts remained patent in 101 of these and occluded in 84; of these, a major amputation was subsequently necessary in 42 cases. Thus, 143 limbs were salvaged (77·29 per cent). Terminal ischaemic changes, ulceration or gangrene were present in 69 limbs, in which 30 grafts remained patent and 35 out of 69 (50·73 per cent) limbs were salvaged. It was of interest that, as indicated in an earlier study, subsequent failure of a graft does not always necessitate amputation. Therefore, in spite of late graft failure, a functioning limb may remain, albeit with some degree of vascular insufficiency (Baddeley et al., 1970).

Complications of surgery

Reports in the literature are scarce, but our records revealed that potentially avoidable complications account for significant morbidity and should receive further attention. Graft patency was not affected by these complications.

Wound complications

Very few wounds discharged frank pus. The incidence of other complications was as follows: sepsis, sloughing, lymphorrhoea and delayed healing, 19·55 per cent (61 limbs); leg oedema, 17·67 per cent (54 limbs); saphenous neuralgia, 3·2 per cent (10 limbs); pulmonary embolism, 2·9 per cent (9 patients); DVT (confirmed), 0·64 per cent (2 limbs); postoperative bleeding, 0·64 per cent (2 limbs).

The site and size of the graft had no relation to the relevance of complications, but oedema was most common following anastomosis below the knee joint (23 out of 107 grafts).

Concomitant sympathectomy

In 68 limbs lumbar sympathectomy was performed at the same time as reconstructive surgery. Numbers are too small for useful comparison, however, but preliminary analysis indicates that patency was less influenced by sympathectomy than by the state of popliteal run-off, graft diameter and the level of the anastomosis.

Postoperative anticoagulant therapy

Phenindione or warfarin therapy was begun 48 h postoperatively and continued without interruption after 100 operations. Unfortunately, selection was uncontrolled, but marginal benefits were apparent where run-off was moderate and veins were less than 5 mm in diameter.

Associated disease

Of 213 cases operated on, diabetes was present in 14·5 per cent, ischaemic heart disease in 59·6 per cent, hypertension in 38·1 per cent and 8·1 per cent had sustained cerebrovascular accidents. As might be expected, the outlook is not quite as satisfactory when widespread disease is present, with an overall patency rate of approximately 50 per cent, as indicated in *Table VIII*. However, in view of the low operative mortality rate these associated conditions are certainly not contraindications to reconstructive surgery.

Table VI: PATENCY, SITE OF ANASTOMOSIS AND CALIBRE OF GRAFT

Anastomosis level	Diameter of graft (mm)	No. grafts	Occluded	Patency No.	%
Above-knee	<5	21	8	13	61·9
Above-knee	>5	170	64	106	62·36
At knee	<5	2	1	1	50.00
At knee	>5	12	4	8	66·6
Below-knee	<5	18	13	5	27·78
Below-knee	>5	89	42	47	52·81

Table VII: PATENCY RELATED TO RUN OFF STATUS AND LEVEL OF GRAFT INSERTION

Run-off	Anastomosis level	No. grafts	Occluded	Patency No.	%
Good	Above-knee	80	23	57	71·25
	Below-knee	35	19	16	45·71
Moderate	Above-knee	46	17	29	63 09
	Below-knee	27	14	13	48·14
Poor	Above-knee	22	11	11	50·00
	Below-knee	24	18	6	25 00

Table VIII: ASSOCIATED DISEASE AND GRAFT PATENCY

Disease	No. grafts	Occluded grafts	Patency No.	%
Cerebrovascular accident	17	8	9	52·94
Diabetes	31	15	16	51·61
ECG change	125	44	79	63 20
Hypertension (>95 mmHg systolic)	80	38	42	52 50
Other (mainly DU)*	46	25	21	45·64

* Two with raised cholesterol, one polycythaemia rubra vera.

Discussion

Our results reaffirm that the reversed saphenous vein graft currently remains the best reconstructive procedure for femoropopliteal occlusive disease. Our 5-year patency is higher than that in our earlier series (Baddeley et al., 1970) and that reported by De Weese and Robb (1977) but it remains lower than in some other series (Darling et al., 1967; Cutler et al., 1976). There is general agreement that run-off is most important and this series confirms this view. Cutler et al. (1976) found no significant difference between patency rates for grafts inserted for mild ischaemic symptoms or for advanced disease, the determining factor being vessel run-off.

Other graft materials are currently being evaluated, but few of these have equalled, let alone surpassed, the results of saphenous vein grafts. DeBakey et al. (1973) quote a 70 per cent 5-year patency with Dacron prostheses in a large series, as does Reichle (1978). However, this has not been the general experience, and only 50 per cent of Dacron prostheses remained patent in the series reported by Stephen et al. (1977). Veith et al. (1978) found comparable patency rates between PTFE and autogenous vein grafts after 14 months, but the late results of the former have been disappointing. Interestingly, combined Dacron–vein grafts have a 71 per cent 5-year patency in a short series of 29 cases reported by Friedmann et al. (1976). These grafts may be useful if the saphenous veins are inadequate.

We have reported a low 5-year mortality of 14·6 per cent whereas reports from others have quoted considerably higher mortality rates of 25 per cent, 38 per cent and 48 per cent respectively at 5 years (DeWeese and Robb, 1977; Myhre, 1977; Alinaji et al., 1978).

The best results are obtained by using large calibre veins above the knee joint; fortunately, 75–80 per cent of cases are suitable for this purpose. Regrettably, results are much less satisfactory with below-knee grafts and we do not agree that implantation is beneficial and should be routine (Sabga et al., 1968). In our experience the disadvantage of the graft kinking across the knee joint outweighs the risk of progressive distal popliteal occlusive disease. Perhaps a suitable compromise should be graft insertion at the knee joint. Like Darling et al. (1967), we feel that graft failure is usually related to progressive distal atherosclerosis; however, we have occasionally seen gangrene develop in limbs where the graft remained pulsatile. Serial arteriography indicated progressive occlusion of run-off arteries. Although not routine, regular arteriograms (Dhall and Mayor, 1978) or ultrasonics (Taylor and Fox, 1977) may predict potential graft failure.

Our limb salvage rate (77 per cent) compares favourably with other series and we re-emphasize that a temporarily functioning graft may still prevent the loss of a limb even after the graft occludes. Five-year patency rates of grafts inserted for limb salvage were at least 60 per cent in series reported by O'Donnell et al. (1977) and Logerfo et al. (1977), but it is not clear from their papers whether the term 'limb salvage' is only applied to patients with advanced ischaemia.

The major problem in management is how to maintain graft patency and prevent distal progressive occlusive disease. We can draw no valid conclusions on the role of anticoagulants or sympathectomy in our series and other reports vary (Buda et al., 1976; Cutler et al., 1976). Studies with antiplatelet drugs may give hope for the future. However, we agree that complete cessation of smoking is mandatory (Myers et al., 1978) and research should continue to be guided towards elucidating the basic mechanisms of atherosclerosis and blood clotting and the prevention of complications in these patients (Harris et al., 1978).

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References

ALINAJI A., BARKER L. F., BURKOWITZ H. D. et al. (1978) Femoro-popliteal vein grafts for claudication. Analysis of 100 consecutive cases. *Ann. Surg.* **188**, 79–82.

BADDELEY R. M., ASHTON F. and SLANEY G. (1968) Comparison of autogenous vein bypass grafts with 'patch' angioplasty for short femoro-popliteal occlusions. *Surg. Gynecol. Obstet.* **127**, 503–508.

BADDELEY R. M., ASHTON F., SLANEY G. et al. (1970) Late results of autogenous vein bypass grafts in femoro-popliteal arterial occlusion. *Br. Med. J.* **1**, 650–656.

BUDA J. A., WEBER C. J., MCALISTER F. F. et al. (1976) Factors influencing patency of femoro-popliteal artery bypass grafts. *Am. J. Surg.* **132**, 8–12.

CUTLER B. S., THOMPSON J. E., KLEINSASSER L. J. et al. (1976) Autologous saphenous vein femoro-popliteal bypass; analysis of 298 cases. *Surgery* **79**, 325–331.

DARLING R. C., LINTON R. R. and RAZZUK M. A. (1967) Saphenous vein bypass grafts for femoro-popliteal occlusive disease: a reappraisal. *Surgery* **61**, 31–40.

DEBAKEY M. E., NOON G. P., DANIELL M. B. et al. (1973) Dacron velour prosthesis; analysis of 425 femoro-popliteal bypass grafts. Presentation at the International Cardiovascular Society, Barcelona, Spain, 22–29 September.

DEWEESE J. A. and ROBB C. G. (1977) Autogenous vein grafts ten years later. *Surgery* **82**, 775–784.

DHALL D. P. and MAYOR G. E. (1978) Long term behaviour of reversed saphenous vein grafts for advanced femoro-popliteal disease. *Surg. Gynecol. Obstet.* **146**, 241–243.

FRIEDMANN P., DELAVRENTIS D. A. and RHEE S. W. (1976) The sequential femoro-popliteal bypass graft: a five-year experience. *Am. J. Surg.* **131**, 452–456.

HARRIS P. L., HARVEY D. R. and BLISS B. P. (1978) The importance of plasma, lipid, glucose, insulin and fibrinogen in femoro-popliteal surgery. *Br. J. Surg.* **65**, 197–200.

LOGERFO F. W., CORSON J. D. and MANNICK J. A. (1977) Improved results with femoro-popliteal vein grafts for limb salvage. *Arch. Surg.* **112**, 567.

MYERS K. A., KING R. B., SCOTT D. F. et al. (1978) The effect of smoking on the late patency of arterial reconstructions in the legs. *Br. J. Surg.* **65**, 267–271.

MYHRE H. O. (1977) Bypass grafting for femoro-popliteal atherosclerosis. *Acta Chir. Scand.* **143**, 109–113.

O'DONNELL J. A., BRENER R. J., BRIEF D. K. et al. (1977) Realistic expectations for patients having lower extremity bypass surgery for limb salvage. *Arch. Surg.* **112**, 1356–1363.

REICHLE F. A. (1978) Criteria for evaluation of new arterial prostheses by comparing vein with Dacron femoro-popliteal bypasses. *Surg. Gynecol. Obstet.* **146**, 714–720.

SABGA G. A., FERRATO P. J., YOUNG W. V. JUN. (1968) Comparison of the long term and the short term results of saphenous vein bypass grafts with distal detachments above and below the knee. *Vas. Surg.* **2**, 135.

STEPHEN M., LOEWENTHAL J., MILES LITTLE J. et al. (1977) Autogenous veins and velour Dacron in femoro-popliteal arterial bypass. *Surgery* **81**, 314–318.

TAYLOR R. S. and FOX N. D. (1977) Ultrasonic prediction of graft failure. *J. Cardiovasc. Surg.* **18**, 309–316.

VEITH F. J., MOSS C. M., FELL S. C. et al. (1978) Comparison of expanded PTFE and vein grafts in lower extremity arterial reconstruction. *J. Cardiovasc. Surg.* **19**, 341–344.

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Fine needle catheter jejunostomy—an assessment of a new method of nutritional support after major gastrointestinal surgery

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SUMMARY

The results of our experience with the technique of fine needle catheter jejunostomy and early postoperative feeding through the catheter over a 12-month period are presented. Of the 43 patients who had the catheter inserted, 27 (63 per cent) completed a course of feeding with an elemental diet without complications, 3 (7 per cent) were not fed for different reasons and 13 (30 per cent) developed complications that led to temporary or permanent cessation of the feeding. One patient in this group died of inhalation pneumonia.

The voluntary food intake of 12 of the patients who were fed by jejunostomy after major colorectal surgery was assessed daily for 2 weeks after operation and compared with that of 12 control patients who did not have nutritional support. No significant difference in voluntary food intake was found between the two groups.

The changes in body composition and plasma proteins and the clinical outcome of 20 of the patients fed by jejunostomy after major colorectal surgery were also compared with those of 20 matched controls. Body weight and lean body mass (as assessed by total body potassium and arm muscle circumference) and plasma prealbumin fell significantly in the control patients but not in those fed by jejunostomy. However, plasma transferrin decreased in both groups and there was no significant difference in clinical outcome in terms of complication rate or duration of postoperative hospital stay.

The study would suggest that this technique of jejunostomy feeding should be reserved for selected cases where it may prove to be of real value, rather than being used routinely.

THE provision of nutritional support after major surgery either by intravenous nutrition (Collins et al., 1978) or by administration of an elemental diet through a nasogastric tube (Sagar et al., 1979) can prevent postoperative nitrogen loss and appears to have some clinical benefits. However, the routine administration of intravenous nutrition after surgery is expensive and difficult in practice. Nasogastric feeding, though cheaper and relatively simpler, may not be acceptable to many patients for more than a few days. A jejunostomy performed at the conclusion of the main operation provides an alternative route of administering the nutrients, and in recent years the relatively simple technique of fine needle catheter jejunostomy has been described and favourable results reported (Delany and Garvey, 1973; Delany et al., 1977).

This present prospective study was carried out with a view to assessing: (*a*) the safety and simplicity of the technique; (*b*) the effect of feeding through the jejunostomy on postoperative voluntary food intake; (*c*) the effect on nutritional status in terms of lean body mass and plasma proteins; and (*d*) whether there are any clinical benefits.

Patients and methods

The study was carried out on patients admitted to the University Department of Surgery at Leeds between January 1978 and January 1979 for elective major colorectal or gastro-oesophageal surgery. The patients were interviewed on admission and informed consent to the study was obtained.

Jejunostomy technique

Forty-three patients had a fine needle catheter jejunostomy inserted at the time of surgery using the method described by Delany et al. (1977). Essentially this consists of creating a submucosal tunnel about 10 cm long in a loop of proximal jejunum, using a 5·1-cm stainless-steel needle with an internal diameter of 1·5 mm (Bard-I-Cath, CR International Ltd), and threading a fine plastic catheter, 40 cm long with an external diameter of 1·5 mm and an internal diameter of 1·0 mm (Vigon Umbilical Catheter, Vigon UK Ltd, Middlesex), through it into the jejunum. The needle is withdrawn over the catheter and a purse-string suture inserted in the jejunal wall around the catheter. Using the same needle the catheter is threaded through the anterior abdominal wall; finally the loop of jejunum is attached to the parietal peritoneum and the catheter fixed to the skin.

Management of jejunostomy feeding

Postoperatively the patients were assessed daily to determine when feeding through the jejunostomy catheter could be started. In general, feeding was initiated as soon as was practical (usually within 48–72 h after operation), provided that the general condition of the patient was satisfactory and abdominal distension and vomiting were absent. Just before feeding, 5 ml of Gastrografin were injected into the jejunostomy catheter and an abdominal X-ray taken to confirm the position of the catheter in the bowel lumen.

An elemental diet (Flexical, Mead Johnson Laboratories) was used for the jejunostomy feeding: 1000 ml of the reconstituted diet contain 22·5 g of protein equivalent, 152·5 g of carbohydrate and 34·0 g of fat and provide 1000 kcal (4·2 MJ) of energy in addition to essential minerals and vitamins. At 'normal' strength the diet has an osmolality of 550 mmol/kg water. However, when feeding was first started, a half-strength diet (½ kcal/ml) was given at the rate of 30 ml/h for the first 24 h. If this was tolerated, the volume and strength were gradually increased until a full regimen of 2000–3500 kcal/day was achieved, depending on the size and estimated requirements of the patient. A McGaw N7922 volumetric infusion pump (Imed Corporation, San Diego, California) was used to deliver the diet.

Assessment of voluntary food intake

To examine the effect of jejunostomy feeding on oral intake we studied the voluntary food intake (VFI) in 12 patients who were fed by jejunostomy after major colorectal surgery and in 12 control patients who had similar surgery but were not given any nutritional support. The daily VFI in terms of energy was assessed over a 2-week period after operation using the weighed inventory method (Marr, 1971; Hackett et al., 1979) and a standard food table (McCance and Widdowson, 1973).

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The home VFI was assessed by a dietary history technique similar to that described by Burke (1947), and the daily postoperative VFI was expressed as a percentage of the home intake, since it has previously been shown that a close correlation exists between the maximum postoperative VFI attained and the home VFI (Hackett et al., 1979).

Assessment of nutritional status
Twenty of the 43 patients who had the jejunostomy inserted were matched in a prospective way for sex, age, body weight, preoperative weight loss (as a percentage of recalled pre-illness weight), diagnosis and extent of surgery (all had colorectal surgery) with 20 control patients who were not given postoperative nutritional support. Both groups of patients were otherwise managed in a similar manner, and were allowed to start eating or drinking when their clinical progress permitted. The effect of jejunostomy feeding on nutritional status and clinical outcome was studied.

Body composition measurements: All the patients had the following measurements taken just before surgery and repeated at 2 weeks after surgery: (*a*) body weight; (*b*) body fat, as calculated from measurement of the thickness of the biceps, triceps and subscapular skinfolds, using the method of Durnin and Womersley (1974); (*c*) arm muscle circumference (AMC), derived from the measurement of the mid-arm circumference (MAC) and the triceps skinfold (t) where $AMC = MAC - \pi t$; (*d*) total body potassium (TBK), determined by measuring the activity of the naturally occurring radioisotope ^{40}K using a whole body counter.

Plasma protein measurements: Venous blood samples were taken (between 0800 h and 1000 h) before operation and 14 days after operation in both groups of patients. Normal values for plasma proteins were obtained from members of hospital staff or patients with insignificant problems. Plasma transferrin and prealbumin (markers of malnutrition) and α_1-antichymotrypsin (an acute phase protein) were determined by radial immunodiffusion technique (Young et al., 1978).

Statistics
The mean changes in the various parameters of body composition for the two groups of patients were calculated, together with the 95 per cent confidence limits.

For analysis of the postoperative voluntary food intake and plasma protein levels, Student's t test was used.

Results

Clinical material

Over the 12-month study period 43 patients had a needle catheter jejunostomy inserted while undergoing major gastrointestinal surgery. The diagnosis and extent of surgery performed in these patients are shown in *Table I*. Five patients underwent gastro-oesophageal resection and 38 underwent colorectal resection.

Table I: DIAGNOSIS AND EXTENT OF SURGERY IN PATIENTS STUDIED

	No. of patients
Total gastrectomy (carcinoma of stomach)	3
Gastro-oesophagectomy (carcinoma gastro-oesophageal junction)	2
Abdominoperineal excision of rectum (10 carcinoma of rectum + 1 ulcerative colitis)	11
Proctocolectomy (ulcerative colitis)	1
Subtotal colectomy (2 carcinoma of colon + 2 ulcerative colitis)	4
Anterior resection (carcinoma of rectum)	10
Hartman's resection (carcinoma rectosigmoid junction)	2
Hemicolectomy (carcinoma of colon)	4
Sigmoid colectomy (carcinoma of colon)	6
Total	43

Outcome of jejunostomy feeding and complications

The outcome of feeding through the catheter jejunostomy in the 43 patients is shown in *Table II*. Three patients had a catheter inserted but were not fed postoperatively. One sustained a massive pulmonary embolus on the second postoperative day and died 2 days later. The second patient had severe respiratory problems in the early postoperative period, requiring a period of positive pressure ventilation in the intensive care unit, as well as a severe ileus which precluded feeding through the jejunostomy. In the third patient the catheter was shown to be lying outside the bowel on routine X-ray with Gastrografin. The catheter was withdrawn and the patient suffered no ill effect.

Table II: OUTCOME OF JEJUNOSTOMY FEEDING IN 43 PATIENTS

	No. of patients
Patients who had jejunostomy catheter but not fed (includes 1 death due to pulmonary embolus)	3
Feeding discontinued completely because of vomiting, abdominal distension or pain (includes 2 deaths)	8
Feeding discontinued temporarily because of nausea, vomiting, abdominal distension, but resumed after short rest	4
Feeding discontinued because catheter pulled out accidentally	1
Course of feeding completed as planned	27
Total	43

Feeding was discontinued in 6 patients because of vomiting, abdominal distension and/or abdominal pain that was thought to be related to the jejunostomy feeding. Two other patients died in the course of feeding. One of these was a 75-year-old woman who, 5 days after anterior resection of a rectal carcinoma, became confused and inhaled vomit during the night; in spite of intensive treatment she died 10 days later of her chest complications. The second patient was another 75-year-old woman who underwent abdominoperineal excision of the rectum for carcinoma. She also was rather confused postoperatively but seemed satisfactory in every other respect. Four days after surgery she suddenly vomited during the night and sustained a cardiac arrest shortly afterwards. The precise cause of death in this second case was not known as permission for a post-mortem examination was refused, and inhalation of vomit as a primary cause remained a possibility.

Four patients developed vomiting and/or abdominal distension in the early stages of feeding but these complications settled when feeding was discontinued for a short period (2–3 days) and it was possible to resume feeding up to the fourteenth postoperative day in these patients.

In one patient the jejunostomy catheter was pulled out accidentally 10 days after gastro-oesophagectomy and feeding was therefore discontinued. Twenty-seven patients completed a planned course of feeding until the second week after operation.

In all but one patient no difficulty was encountered in removing the catheter when this was no longer required. One patient had to be sedated and forceful traction was required to withdraw the catheter; when it was removed the end was found to be tied in a knot.

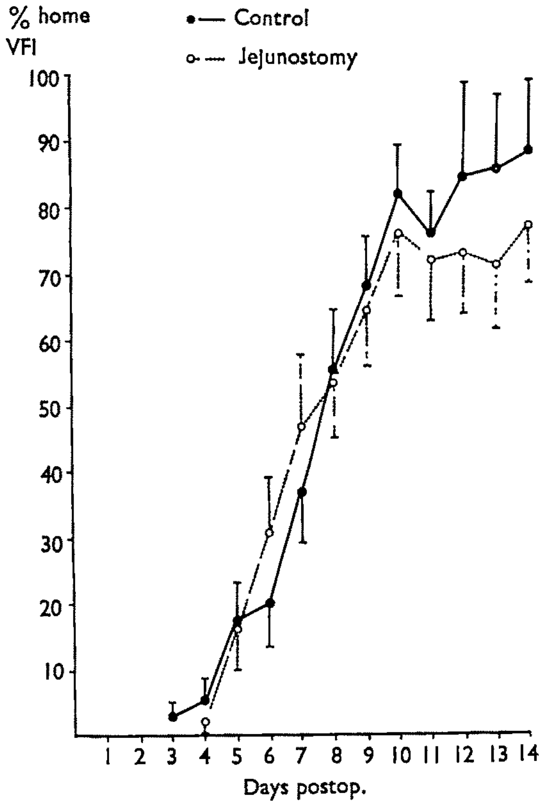

Fig. 1. Voluntary food intake (VFI) in the two groups of patients, expressed as a percentage of the home voluntary food intake, during the first 14 days after operation (mean ± s.e. mean).

One patient developed minor sepsis at the site of the catheter after its removal, but this settled without any active treatment. None of the patients developed a fistula.

Calories achieved

In those 27 patients who completed the course of postoperative feeding as planned, feeding was initiated on average 3·0 ± 1·8 days (mean ± 1 s.d.) after surgery and lasted for a mean period of 10·9 ± 2·7 days. Over this period the average intake through the jejunostomy catheter was 1692 ± 270 kcal/day (29·9 ± 8·2 kcal kg body weight^{-1} day^{-1}). There was a significant correlation between the average daily energy intake through the jejunostomy and the duration of feeding ($r = 0{\cdot}63$, $P < 0{\cdot}01$).

Effects of jejunostomy feeding on voluntary food intake

Fig. 1 shows the mean daily voluntary food intake (expressed as a percentage of the home intake before surgery) of the subgroup of 12 patients fed by jejunostomy and that of the group of 12 control patients. Both groups underwent comparable colorectal surgery. It can be seen that in both groups of patients the VFI increased gradually until it reached a peak round about the tenth postoperative day after which it remained relatively constant. There was no significant difference in the mean food intake between the two groups for any of the 14 postoperative days ($P > 0{\cdot}05$).

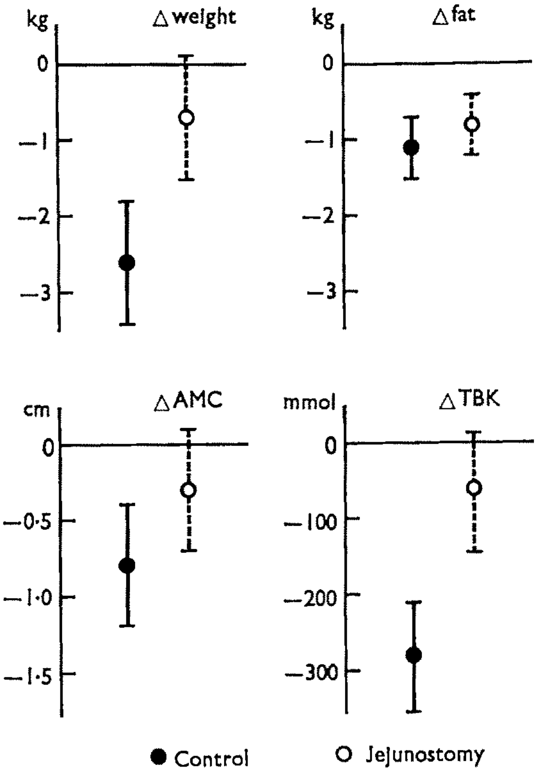

Fig. 2. Mean changes (with 95 per cent confidence limits) in body weight, body fat, arm muscle circumference (AMC) and total body potassium (TBK) in the two groups of patients.

Table III: MATCHING DATA IN THE TWO GROUPS OF PATIENTS IN WHOM BODY COMPOSITION AND PLASMA PROTEIN MEASUREMENTS WERE MADE

	Control	Jejunostomy
Male : Female	10 : 10	10 : 10
Age (yr)	62·8 ± 9·9	64·6 ± 9·4
Height (cm)	164·3 ± 8·7	163·1 ± 10·7
Body weight (kg)	62·1 ± 13·7	58·2 ± 12·8
Preop. weight loss (%)	8·7 ± 7·2	8·1 ± 7 8

Values are mean ± 1 s.d.

Effect on body composition

Table III shows the sex distribution, mean age, height, body weight and percentage weight loss in the subgroup of 20 patients whose body composition was measured, compared to those of 20 control patients. All these parameters were very similar in both groups. The diagnosis and extent of surgery were also closely matched in the two groups.

Fig. 2 shows the mean changes (with 95 per cent confidence limits) in body weight, body fat, arm muscle circumference (AMC) and total body potassium (TBK) in the two groups over the 2-week period. There was a mean loss of 2·5 kg in body weight in the control patients, but no significant loss in those receiving the elemental diet. There was a smaller but significant loss of body fat (1·1 and 0·8 kg respectively) in both groups. AMC was decreased significantly in

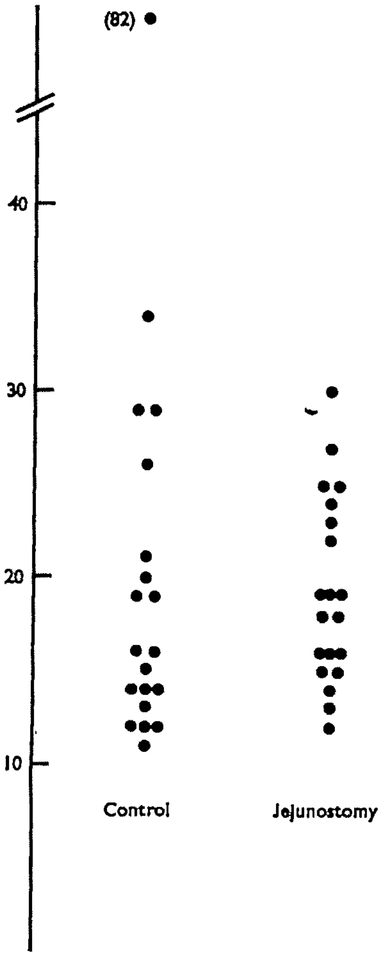

Fig. 3. Duration of hospital stay (in days) after surgery in the two groups of patients.

the control group, but not in the elemental diet group. Similarly, there was a significant loss in TBK (285 mmol) in the control group but not in the elemental diet group.

These results show that the loss of body weight and lean body mass was prevented in those patients who received the elemental diet through the jejunostomy.

Effect on plasma proteins

The mean concentrations of proteins in preoperative and postoperative plasma samples for each of the two groups of patients are compared with normal values in *Table IV*. Mean values for transferrin and prealbumin before surgery were not significantly different from normal. Lowest concentrations of these proteins occurred in patients with the greatest preoperative weight loss.

Two weeks after surgery mean plasma transferrin and prealbumin in the control group were lower than normal. However, in the jejunostomy group the mean prealbumin was restored to the preoperative concentration, and was decreased only in 6 patients (4 who had less than 65 per cent of the mean intake of elemental diet, 1 with sepsis, and 1 with unexplained pyrexia).

Table IV: MEAN VALUES (±s.e. mean) FOR PLASMA TRANSFERRIN, PREALBUMIN AND α_1-ANTICHYMOTRYPSIN IN NORMAL INDIVIDUALS AND IN PATIENTS BEFORE SURGERY AND 2 WEEKS AFTER SURGERY

Group	Trans. (mg/100 ml)	Prealb. (mg/100 ml)	α_1-Antichy. (mg/100 ml)
Normals ($n = 12$)	285±11	28·5±1·2	44±3
Controls ($n = 20$)			
Preop.	279±11	23·9±1·7	76±4†
Postop.	226±9* −53‡	20·4±1·5* −3·5‡	114±6† +38‡
Jejunostomy ($n = 20$)			
Preop.	264±13	24·4±1·7	74±4†
Postop.	226±14* −41‡	24·2±1·7 −0·2	110±6† +36‡

Trans., Transferrin; Prealb., prealbumin; α_1-Antichy., α_1-antichymotrypsin.
* Mean values lower than normal, $P<0{\cdot}005$.
† Mean values higher than normal, $P<0{\cdot}001$.
‡ Mean changes significantly greater than zero, $P<0{\cdot}01$.

Table V: POSTOPERATIVE COMPLICATIONS IN 20 CONTROL PATIENTS AND 20 PATIENTS FED BY JEJUNOSTOMY

	Control ($n = 6$)	Jejunostomy ($n = 7$)
Anastomotic leak+local abscess	1	1
Abdominal wound infection	1	—
Ileus	—	3
Chest infection	1	—
Urinary tract infection	2	3
Urinary retention	2	1
Cardiac failure	1	—
Cerebrovascular accident	1	—
Total complications	9	8

In contrast, the mean transferrin level was lower than normal, as for controls.

The mean concentration of α_1-antichymotrypsin was above normal in both groups. Following the 2-week period, there were comparable increases in the mean values for both groups, suggesting a similar response to sepsis and trauma.

Clinical effects

Fig. 3 shows the duration of stay in hospital after surgery (in days) in the two groups of patients. One patient in the control group had a cerebrovascular accident and stayed in hospital for 82 days, otherwise, the duration of stay in hospital was similar in both groups. Eight patients in the control group and 3 patients in the elemental diet group went home by the fourteenth postoperative day. It is conceivable that the presence of the jejunostomy may have delayed the discharge of patients in this group by a few days though every effort was made at the time of the study to prevent this from happening. However, since the feeding was terminated at 2 weeks, this cannot be held responsible for delay in hospital discharges beyond the 2-week period.

Table V shows the main complications that occurred in the two groups of patients. Though the number of complications was roughly equal—9 complications in 6 control patients and 8 complications in 7 patients fed by jejunostomy—the type of complication differed. In particular, there were 3 patients in the group fed by jejunostomy who had a prolonged ileus (>6 days), while this complication was not seen in the control group.

Discussion

This study shows that the actual technique of needle catheter jejunostomy is simple and safe to perform. Of the 43 catheters inserted, one was pulled out accidentally during feeding and in another patient the catheter became dislodged from the bowel, but this was detected on routine X-ray with Gastrografin. There were no instances of leakage of the nutrient solution into the peritoneal cavity, fistula formation or intestinal obstruction due to adhesions at the jejunostomy catheter site, and none of our patients required reoperation for complications resulting from the catheter.

The inherent safety of the technique is supported by other authors. Page et al. (1978) report 4000 patient-days of catheter jejunostomy feeding in 181 patients with only 2 major complications (1·1 per cent) requiring reoperation. Delany et al. (1977), in a series of 115 patients, had 4 cases in which the catheter became dislodged and 2 of these came to surgery. In the latter cases the catheter was secured to the bowel wall but the bowel was not sutured to the parietal peritoneum. It seems important, therefore, to suture the bowel to the peritoneum in all cases to prevent dislodgement of the catheter and subsequent instillation of the nutrient solution into the peritoneal cavity.

Though the actual technique of needle catheter jejunostomy is simple and relatively safe, the delivery of the elemental diet through the catheter requires great care as complications are not uncommon and may in certain instances be serious. In our 43 patients, 27 (63 per cent) completed a course of feeding without interruption, but in 12 (28 per cent) the feeding was either temporarily or permanently stopped because of complications which seemed to be related to the feeding. The commonest cause was abdominal distension and vomiting. Two patients died during the course of feeding in this series: both were elderly female patients who were confused postoperatively. One died of aspiration pneumonia, but the cause of death in the second one was uncertain though she was reported as having vomited before sustaining a cardiac arrest. Both these patients vomited during the night and the vomitus, described as 'clear bile', did not appear to contain the elemental diet. Intragastric administration of elemental diets has been shown to cause delay in gastric emptying (Bury and Jambunathan, 1974), but the effect of giving the diet intrajejunally on gastric motility and gastric and biliary secretion is not known, though there seems to be little effect on pancreatic secretion (Ragins et al., 1973; Kelly and Nahrwold, 1976). It may be that some of the problems with abdominal distension and vomiting in our patients were due to our attempt at starting the feeding through the jejunostomy catheter too early.

It was interesting to find that the administration of the elemental diet via the jejunostomy catheter did not depress oral food intake, as compared with control patients who did not receive supplementary feeding by jejunostomy. The net energy intake (and protein intake) was therefore significantly increased (more than doubled) in those patients with the jejunostomy feeding, and the nutritional benefits are reflected in maintenance of body weight and of lean body mass as assessed by total body potassium and arm muscle circumference.

We have previously found that clinical improvement has been associated with increases in visceral proteins (Young et al., 1979), and these are intimately involved with host defence and survival. It is therefore encouraging that plasma prealbumin, with a half-life of 2 days, was restored to the preoperative concentration, although transferrin, with a half-life of 8 days, remained low. This suggests that if more calories and nitrogen had been supplied by the jejunostomy feeding, these 'visceral proteins' may have been increased. Evidence for this is suggested by the correlation between the changes in plasma prealbumin concentration and the total amount of elemental diet ($r = 0{\cdot}64$, $P < 0{\cdot}01$).

These changes in plasma proteins are compatible with the clinical observations, notably that there was no advantage in terms of duration of hospital stay after surgery and complication rate in those patients fed by jejunostomy as compared with controls. Our results differ from those of the study reported by Sagar et al. (1979) in which it was shown that administration of an elemental diet into the upper small intestine through a double lumen tube during the first week after surgery is associated with fewer postoperative complications and a shorter stay in hospital in patients undergoing major gastrointestinal surgery.

Our results indicate that there is little justification in the routine use of this technique of postoperative feeding, at least after colorectal surgery. It should be reserved perhaps for selected cases—patients who present for major surgery after significant preoperative weight loss and in whom further weight loss in the postoperative period may be detrimental for their recovery; or patients in whom the surgeon anticipates complications and/or delay in taking nutrients orally. We have found the technique particularly useful in patients undergoing gastro-oesophageal surgery as it is our routine to withhold oral intake in these patients until the integrity of the anastomosis has been checked with a Gastrografin swallow about 10 days after operation. If a leak is demonstrated, the patient can be maintained in a good nutritional state through the jejunostomy feeding while waiting for the leak to close spontaneously.

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References

BURKE B. S. (1947) The dietary history as a tool in research. *J. Am. Diet. Assoc.* **23**, 1041–1046.

BURY K. D. and JAMBUNATHAN G. (1974) Effects of elemental diets on gastric emptying and gastric secretion in man. *Am. J. Surg.* **127**, 59–64.

COLLINS J. P., OXBY C. B. and HILL G. L. (1978) Intravenous amino acids and intravenous hyperalimentation as protein-sparing therapy after major surgery. *Lancet* **1**, 788–791.

DELANY H. M., CARNEVALE N., GARVEY J. W. et al. (1977) Postoperative nutritional support using needle catheter feeding jejunostomy. *Ann. Surg.* **186**, 165–170.

DELANY H. M. and GARVEY J. W. (1973) Jejunostomy by a needle catheter technique. *Surgery* **73**, 786–790.

DURNIN J. V. G. A. and WOMERSLEY J. (1974) Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br. J. Nutr.* **32**, 77–97.

HACKETT A. F., YEUNG C. K. and HILL G. L. (1979) Eating patterns in patients recovering from major surgery—a study of voluntary food intake and energy balance. *Br. J. Surg.* **66**, 415–418.

KELLY G. A. and NAHRWOLD D. L. (1976) Pancreatic secretion in response to an elemental diet and intravenous hyperalimentation. *Surg. Gynecol. Obstet.* **143**, 87–91.

MCCANCE R. A. and WIDDOWSON E. M. (1973) *The Composition of Foods*. Medical Research Council Special Report, Serial No. 297. London, HMSO.

MARR J. W. (1971) Individual dietary surveys: purposes and methods. *World Rev. Nutr. Dietet.* **13**, 105–164.

PAGE C. P., CARLTON P. K., ANDRASSY R. J. et al. (1973) Safety of operative needle catheter gastrointestinal intubation for the administration of elemental diet. Paper presented at the XI International Congress of Nutrition, Rio de Janeiro, Brazil.

RAGINS H., LEVENSON S. M., SIGNER R. et al. (1973) Intrajejunal administration of an elemental diet at neutral pH avoids pancreatic stimulation. *Am. J. Surg.* **126**, 606–614.

SAGAR S., HARLAND P. and SHIELDS R. (1979) Early postoperative feeding with elemental diet. *Br. Med. J.* **1**, 293–295.

YOUNG G. A., COLLINS J. P. and HILL G. L. (1979) Plasma proteins in patients receiving intravenous amino acids or intravenous hyperalimentation after major surgery. *Am. J. Clin. Nutr.* **32**. (In the press.)

YOUNG G. A. and HILL G. L. (1978) Assessment of protein–calorie malnutrition in surgical patients from plasma proteins and anthropometric measurements. *Am. J. Clin. Nutr.* **31**, 429–435.

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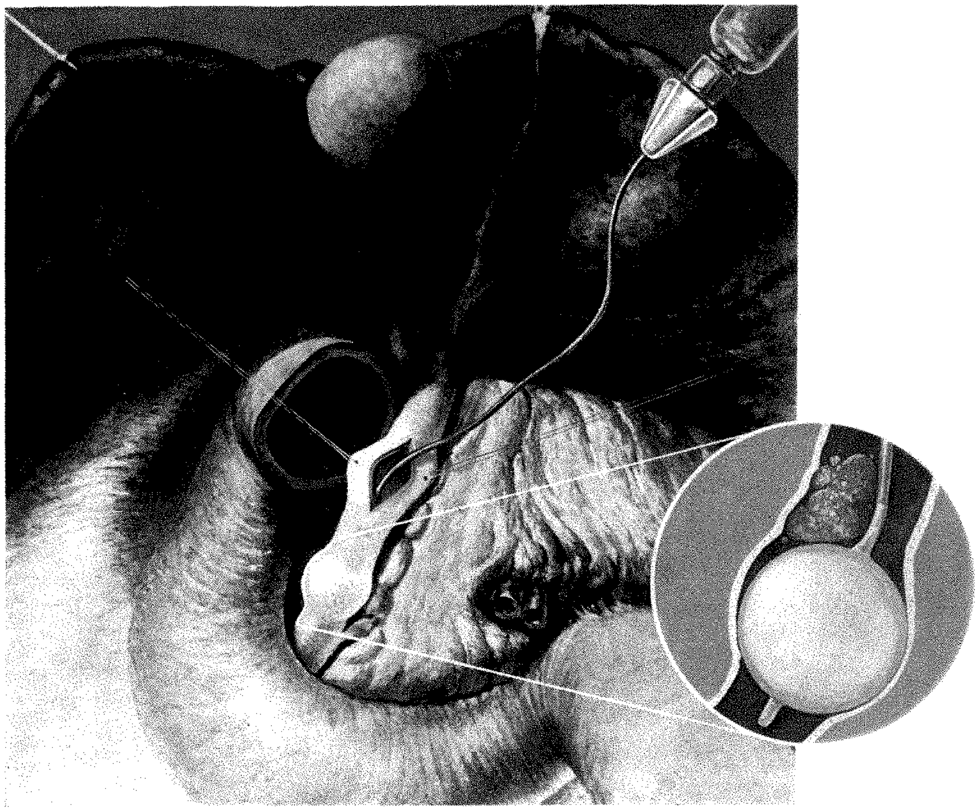

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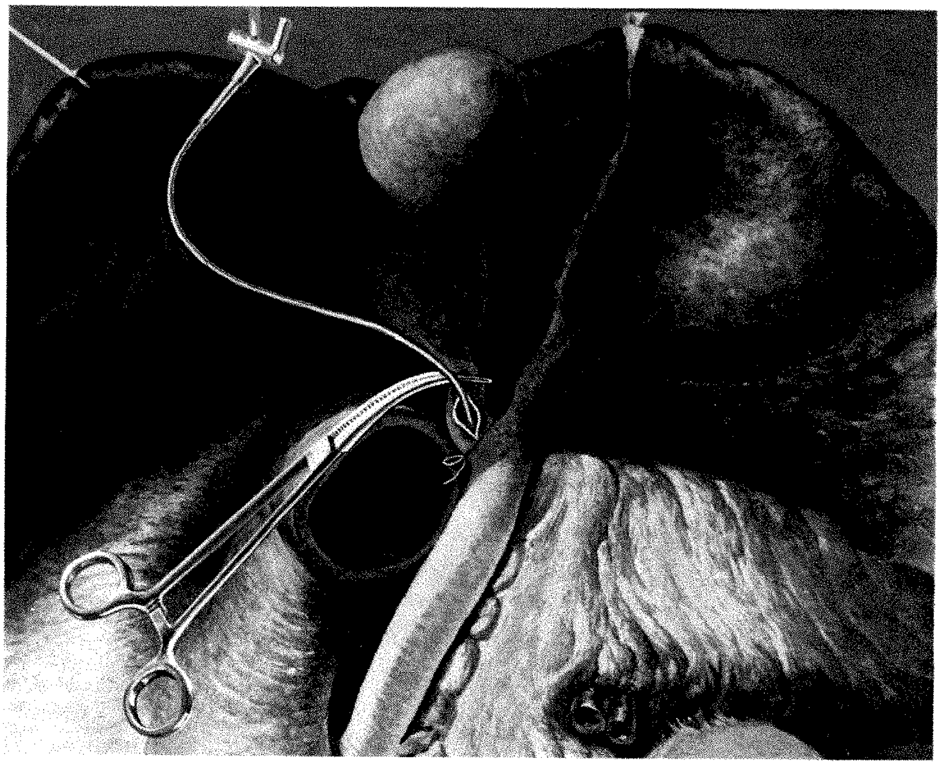

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Lesser curve superficial seromyotomy—an operation for chronic duodenal ulcer

THOMAS V. TAYLOR*

SUMMARY
Lesser curve superficial seromyotomy has been investigated in the dog and in man. The anatomical basis for the operation, which produces an easily performed denervation of the parietal cell mass, is discussed. Acid studies in the dog confirmed that the operation was capable of producing secretory inhibition in keeping with vagotomy of the parietal cell area.

A consecutive series of 25 patients with chronic duodenal ulcer has been treated by lesser curve myotomy without a drainage procedure. The operation has the advantages of being easily performed and the risk of damage to the nerve of Latarjet or of ischaemic necrosis of the lesser curvature is obviated. In 20 insulin tests performed within the first month postoperatively all patients have been negative within the first 75 min and there were 4 late positive responses. Early clinical results have been encouraging, there has been no dumping or diarrhoea and all patients are well. It is suggested that further investigation of lesser curve myotomy is warranted.

HIGHLY selective vagotomy has steadily become established in the treatment of peptic ulceration since it was first performed without a drainage procedure in man (Amdrup and Jensen, 1970; Johnston and Wilkinson, 1970). By 1975 Johnston reported only 17 deaths following 5539 operations carried out in Britain, Scandinavia and the United States, an operative mortality of 0·3 per cent. The rate of recurrent ulceration, in those series with longer follow-up, has been reported at 4·3 per cent by Goligher et al. (1978) and Dorricott et al. (1978) and 5·4 per cent by Stoddard et al. (1978), incidences similar to that following truncal vagotomy and drainage. However, highly selective vagotomy is not without its disadvantages, namely that the operation is tedious and time-consuming to perform, damage to the nerve of Latarjet may produce gastric stasis and there is a small risk of ischaemic necrosis which, when it does occur, is not uncommonly fatal (Newcombe, 1973; Hall et al., 1974; Wyllie, 1974; Halvorsen, 1975).

In the Edinburgh area between 1976 and 1978, 584 elective operations were carried out for duodenal ulceration; 110 of these were highly selective vagotomies and 474 vagotomy and drainage procedures. Thus, highly selective vagotomy has been slow to gain widespread acceptance, accounting for only 18·8 per cent of operations for duodenal ulceration performed in the Edinburgh area. In this study the aim has been to develop an operation which denervates the parietal cell mass, which can be more easily and expeditiously performed and which carries neither risk of damage to the nerve of Latarjet nor of ischaemic necrosis of the lesser curvature.

Anatomical considerations

Considering the anatomy of the vagus nerve, Latarjet (1922), McCrea (1924) and Mitchell (1940) all emphasized that the gastric branches of the nerve of Latarjet, or the greater anterior and posterior gastric nerves, have no predilection to run with the vessels along the walls of the stomach. Mitchell (1940) stated that the nerves can be traced for some distance beneath the serous coat before they sink into the stomach musculature. The present author's anatomical observations have confirmed that these nerves always run superficial to and more obliquely than those major blood vessels leaving the left and right gastric arteries and running along the walls of the stomach from the lesser curve aspect. Any nerves accompanying the vessels are usually sympathetic, a parasympathetic nerve crossing a vessel does so superficially.

Lesser curve myotomy

Based upon these anatomical observations, a method of denervating the parietal cell mass by gastric lesser curve superficial seromyotomy has been devised. In this operation the vagal branches are divided as they run with the serosa along the lesser curvature. The oblique and superficial circular muscle fibres are divided along with the serosa, permitting wide separation of the nerves. Most of the major vessels running along the lesser curvature are left intact, the serosa running superficial to them is divided and the myotomy can be continuous beneath. The nerves of Latarjet need not be identified; they are not at risk of damage during the operation and the integrity of the antral and pyloric innervation is maintained.

The extent of the myotomy running along the lesser curvature from the oesophagogastric junction to the antrocorpus junction is shown in *Fig.* 1. This diagram illustrates the separation of the nerves which must occur along the myotomized segment and the integrity of those two or three major vessels proximal to the crow's foot.

Materials, patients and methods

Animal experiments

Experiments were first performed in the dog. A gastric cannula was inserted and pentagastrin infusions were carried out on three separate occasions in 4 dogs. An initial dose of 0·375 $\mu g\ kg^{-1}\ h^{-1}$ was doubled at half-hourly intervals until a dose of 6 $\mu g\ kg^{-1}\ h^{-1}$ was infused. Three separate insulin tests were performed using 0·2 units/kg i.v. Lesser curve myotomy was then carried out and three further pentagastrin and insulin tests were performed more than 1 month postoperatively. Acid output was determined by titration to pH 7·0 using an autotitrator.

Lesser curve myotomy in man

Twenty-five procedures have been performed in man between February 1978 and February 1979. There were 15 males and 10 females aged 42·5 ± 13·5 s.d. years. In each case the diagnosis was made clinically, radiologically at laparotomy and usually by endoscopy. The series is consecutive apart from those patients treated as emergencies with either perforation or haemorrhage. In 3 cases a degree of pyloric stenosis was

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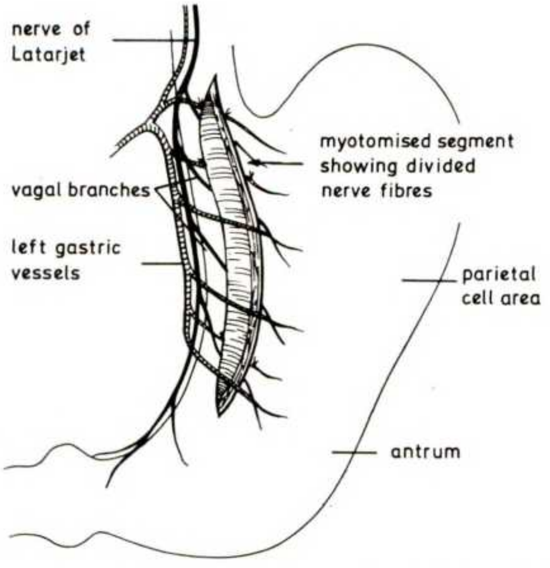

Fig. 1. A diagrammatic representation of the anterior myotomy showing separation of vagal branches but preservation of at least two major blood vessels.

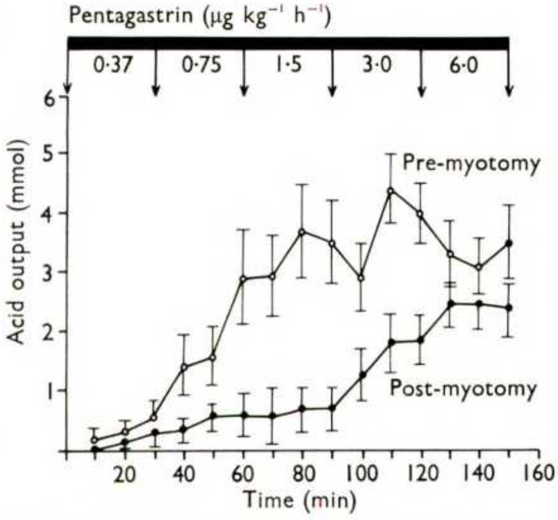

Fig. 2. Acid secretion in response to pentagastrin before and after myotomy in 4 dogs.

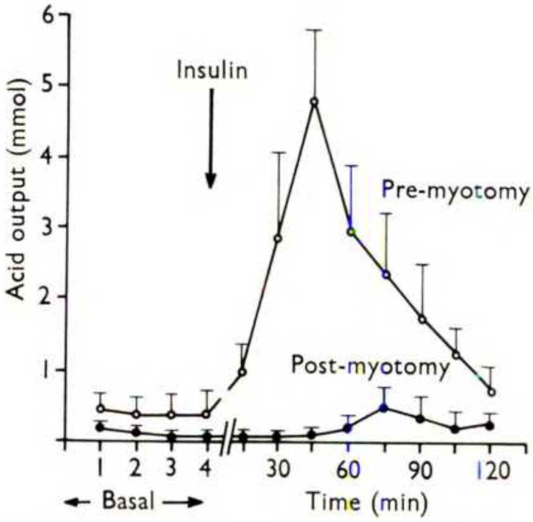

Fig. 3. Acid secretion in response to insulin (0·2 units/kg) before and after myotomy in 4 dogs.

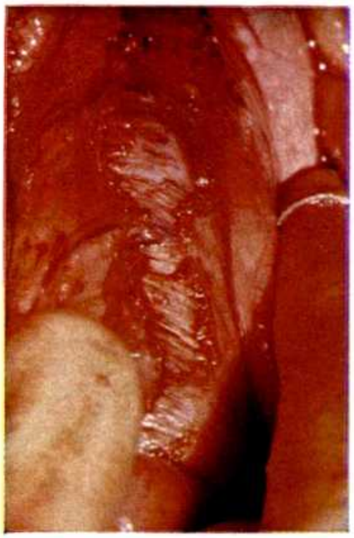

Fig. 4. Myotomized segment showing separation of serosa and superficial circular muscle. The integrity of two blood vessels is shown.

present: in 2 the pylorus was stretched through a gastrotomy and myotomy of the lesser curve was performed and in the third the duodenum split on stretching and pyloroplasty was carried out, the patient then being excluded from the series.

Operative technique

The abdomen was opened through an upper midline incision, the primary pathology and absence of associated pathology were confirmed and the pylorus was assessed for stenosis. The anterior and posterior vagal trunks were identified and mobilized and slings were individually placed around these. The lower 6–7 cm of oesophagus were cleared of any fine strands of vagus. The anterior nerve of Latarjet was first mobilized by dividing the neurovascular bundle which runs across the oesophagogastric junction. These are the only vessels which invariably require division, after which the nerve of Latarjet can be retracted medially and the anterior gastric wall is exposed for commencement of the myotomy.

The serosa and superficial layers of oblique and circular muscle were next incised parallel to the lesser curvature from the oesophagogastric junction down the incisura. The incision in the serosa was initially made by diathermy and then the muscle fibres were divided with scissors. The divided muscle fibres retract widely following gentle displacement with a small pledget. Occasional deeper circular muscle fibres remained intact and then a little bleeding was encountered. The divided vagal branches which run in the superficial serosa at the site of the myotomy became separated by about 1 cm. Where large gastric vessels ran from the left gastric artery and vein to the anterior and posterior walls of the stomach these were in the main carefully preserved, but the myotomy was extended to the tissues lying directly adjacent to these vessels.

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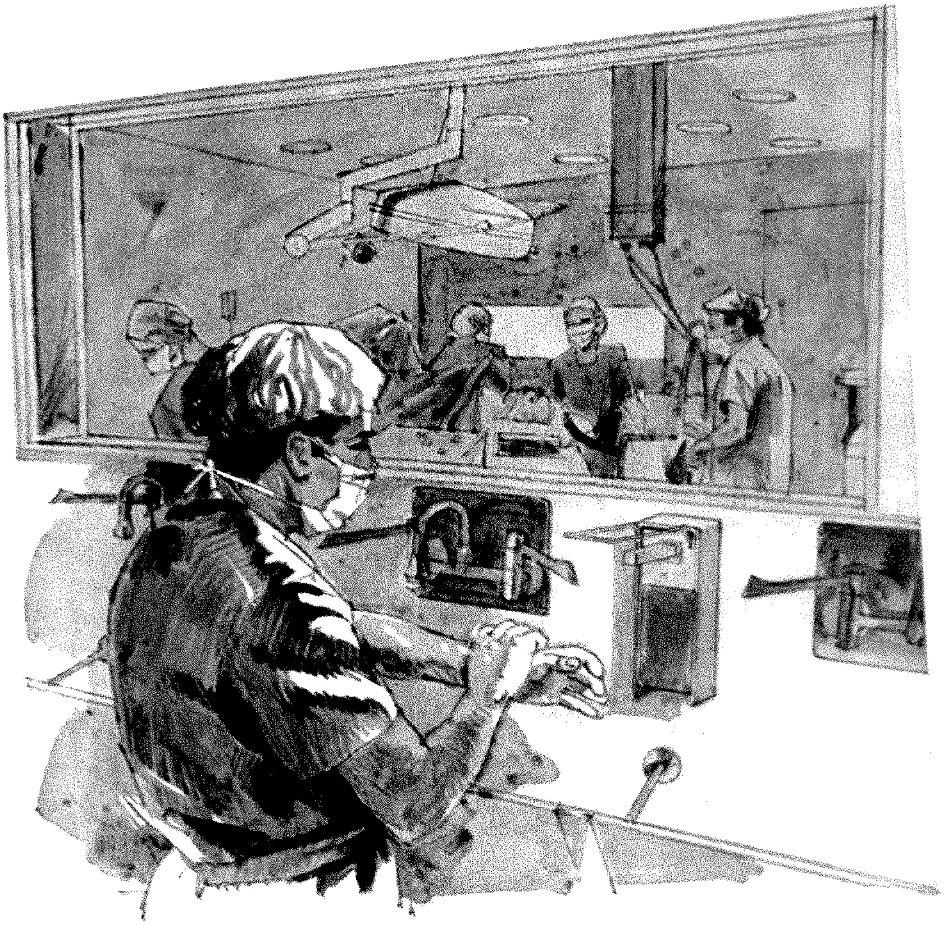

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1) Schneider et al., Chirurg **47,** 185 (1976)
2) McMichan et al., Med. Welt **27,** 233 (1976)

Should a nerve obliquely cross a vessel along the line of myotomy this can usually be seen and the vessel sacrificed. Where a decision was made to divide vessels 'liga clips' were used, but always at least two large vascular bundles were left intact, obviating any risk of ischaemic necrosis of the lesser curvature.

The posterior myotomy was begun from below at the level of the incisura. The avascular plane between the left and right gastric vessels was opened and, in addition, a window was formed in the greater omentum preserving the gastroepiploic arch. The author has found it most convenient to begin the myotomy through the lesser omental opening and to complete it by rotating the stomach medially and extending the myotomy proximally and laterally below the oesophagogastric junction.

Postoperatively a nasogastric tube was used for 48 h after which oral fluids were commenced leading to a light diet by the fourth postoperative day.

Gastric function tests

Pentagastrin stimulation tests were performed preoperatively in all patients. Fasting juice was aspirated and basal secretions collected for 1 h before intramuscular injection of pentagastrin (Peptavlon) 6 μg/kg. Four further 15-min collections of continuously aspirated secretions were carried out. Acid concentration was measured by titration with one-tenth normal sodium hydroxide to pH 7·0 using an autotitrator. Insulin tests have been performed within 1 month in 20 patients and have been repeated in those who have attained 6-month follow-up. These tests have been carried out by an infusion test (Carter et al., 1973) using a dose of 0·04 units $kg^{-1} h^{-1}$ and employing the criteria of Hollander (1946).

Follow-up

Patients were reviewed at 1, 3, 6 and 12 months. Questions were specifically asked from a proforma regarding pain, dyspeptic symptoms, dumping, diarrhoea or other problems. The patients were then graded I–IV on a Visick scale. The follow-up varied in length from 3 months to 1 year.

Results

Animal study

The mean acid output in 4 dogs together with the standard deviation in response to graded doses of pentagastrin is shown in *Fig.* 2. The reduction in acid output shown postoperatively, with its characteristic shift to the right, is in keeping with the observations on acid output after truncal vagotomy in the dog described by Emas and Grossman (1967). The effect of insulin (0·2 units/kg i.v.) on acid output is shown in *Fig.* 3. Three of the dogs showed no rise in acid secretion in response to insulin but 1 showed a late response of very small magnitude.

Human study

There has been no mortality, minimal morbidity and the clinical results have been good, although follow-up is short. Ulcer pain and acid regurgitation have been completely relieved to date. The inpatient stay ranged from 6 to 22 days with a mean of 9·4 ± 3·65 s.d. Normal diet had been resumed by the first review at 1 month in all patients, and bowel habits had remained or returned to normal at this time. There has been no dumping and no postvagotomy diarrhoea.

One patient had symptoms of gastric stasis which spontaneously resolved by 1 month. Wound infection occurred in 3 patients and chest infection in 5. There has been one complication directly attributable to the procedure: the mucosa was perforated in a 48-year-old male who underwent reoperation on the fourth postoperative day. A small hole in the anterior lesser curvature was oversewn and was considered to be due to a diathermy burn. This hazard is avoidable and need not be associated with the procedure. Diathermy is no longer used to divide the muscle fibres and its use is confined to incising and occluding small vessels on the serosa.

Follow-up at 3 months in 20 patients revealed them all to be Visick grade I and those 9 patients reviewed at 6 months and the 3 seen at 1 year remained symptom-free. There has been a total absence of recurrent ulcer symptoms.

Gastric secretion

In 20 patients the mean basal acid output per hour was reduced from 5·0 ± 4·3 s.d. mmol to 0·77 ± 0·66 s.d. mmol in the early postoperative period, a mean reduction of 85 per cent. Using Hollander's criteria for assessment of the insulin tests all patients were negative in the first 75 min after commencement of insulin infusion. Four patients had a late rise in acid concentration of greater than 20 mmol/l between 75 and 120 min after insulin. Those secretory results so far obtained at 6 months after operation show a tendency for reversal from negative to positive. The magnitude of this reversal in terms of acid output appears small and in keeping with that reported by Lyndon et al. (1975) after highly selective vagotomy.

Gastric emptying, both liquid and solid phase, with measurements of early emptying, is being assessed. A double isotope scanning technique for simultaneous study of liquid and solid components of a cornflakes, sugar and milk meal is being used (Heading et al., 1976). This will form the basis of a later study, but there is no evidence of either gastric hold up following myotomy or of rapid early emptying.

Discussion

The animal experiments formed the basis for investigation in man. The pattern of acid secretory inhibition produced by myotomy in response to stimulation by pentagastrin is similar to that in response to histamine and gastrin in dogs after truncal vagotomy (Emas and Grossman, 1967). The secretory output in response to insulin stimulation was similar to that after truncal vagotomy in 3 dogs (Emas and Grossman, 1967), and 1 dog showed a slight rise in acid secretion. Griffiths and Harkins (1957) described a small acid secretory response in 7 of 10 dogs in their experimental study of partial gastric vagotomy, the study which formed the basis of highly selective vagotomy as we know it. The animal experiments described in the present study suggest that the acid secretory inhibition achieved by lesser curve myotomy is comparable with that produced by conventional highly selective vagotomy, at least in the short term.

Despite the physiological advantages of confining vagotomy to the parietal cell area of the stomach, vagotomy and drainage remains the most commonly performed operation for duodenal ulcer. The major objection to highly selective vagotomy raised by surgeons is that the operation is tedious and time-consuming, as every nerve and blood vessel passing on to the lesser curve of the stomach, above the incisura, has to be ligated and divided. Favourable reports of highly selective vagotomy in consecutive series have come from Humphrey et al. (1972), Amdrup et al. (1974), Hallenbeck et al. (1976), Holst-Christensen et al. (1977) and Goligher et al. (1978) and from prospective clinical trials comparing highly selective with other forms of vagotomy (Kennedy et al., 1975; Kronborg and Masden, 1975; Dorricott et al., 1978).

The main advantage of lesser curve myotomy is that it produces a highly selective vagotomy in an expeditiously and easily performed manner. There should be neither risk of damage to the nerve of Latarjet, which need not be identified, nor of ischaemic necrosis of the lesser curvature. Ramstedt in 1912 introduced pyloromyotomy, an operation which carries a mortality of only 0·5 per cent in the neonate (Benson and Lloyd, 1964). Heller (1913) described oesophagomyotomy, which has also stood the test of time and been shown to be intrinsically safe. In lesser curve myotomy the area between oesophagus and antrum is myotomized and there is no reason to believe that myotomy in this situation should be associated with any greater morbidity than has been reported in the other two adjacent sites over the past 65 years. The one complication directly attributable to the operation, that of gastric perforation, was considered to be due to a diathermy burn. Initially the muscle fibres were divided by diathermy; the use of diathermy is now confined to the incision in the serosa and the coagulation of small vessels running along the serosal surface, the muscle fibres are divided by blunt-ended dissecting scissors. The integrity of the mucosa is checked at the end of the operation by introducing air into the stomach and it is currently considered that the risk of perforation is entirely avoidable.

Two major anatomical considerations are fundamental to the success of this procedure. First, that all vagal branches passing to the parietal cell area are divided and, secondly, that the divided nerves do not regenerate. The anatomical descriptions of Latarjet (1922), McCrea (1924) and Mitchell (1940) have been confirmed by our own observations that the branches of the nerves of Latarjet always run superficial to and more obliquely than the major blood vessels along the lesser curvature. Myotomy of the whole lesser curve from the oesophagogastric junction to the incisura must provide separation of all nerve fibres which run with the serosa. Preservation of most of the major vessels does not preclude division of any nerve which might cross these along the line of myotomy, for the serosa over the vessel can be divided without damaging the latter. Following division of the serosa, oblique and superficial circular muscle wide separation of the divided serosa with its related nerves spontaneously occurs, wider separation being easily attained by blunt dissection with a pledget. Regeneration would require sprouting to occur across a 1–2 cm gap and for the minority of efferent nerves to grow along the appropriate axon sheaths. Such efficient nerve regeneration would seem unlikely and indeed acid secretory studies performed up to 1 year after myotomy do not show evidence of a major degree of regeneration. Amdrup and Griffith (1969) stated that in their experience the amount of mucosal reinnervation occurring as a result of the phenomenon of sprouting is insignificant.

The posterior myotomy is not difficult to perform. The posterior vagus runs down behind and separate from the oesophagus and upper gastric wall to the level of the left gastric artery where it becomes closely applied to the lesser curvature (Mitchell, 1940). The proximal end of the posterior myotomy is extended laterally below the oesophagogastric junction. As the nerves of Latarjet do not need to be identified and as adipose tissue does not extend across the gastric walls, obesity is not regarded as a contraindication to this procedure.

Insulin testing performed within 1 month of operation has shown that secretory inhibition at this stage is satisfactory and similar to that reported after highly selective vagotomy. There have been no early positive but four late positive responses, the acid output being comparable to that quoted by Amdrup and Jensen (1970). With increasing periods of time there has been a tendency for reversal of insulin status from negative to positive. The magnitude of this increase in acid output has not been great and appears to be quantitatively similar to that reported by Lyndon et al. (1975).

Although the clinical results following this operation are good and all our patients are well, the follow-up period is currently too short to permit full assessment. The final judgement of this procedure will rest on the incidence of recurrent ulceration. Longer term follow-up of highly selective vagotomy is now emerging, with a reported recurrence rate of 4·3 per cent from Dorricott et al. (1978) and Goligher et al. (1978) and of 5·4 per cent from Stoddard et al. (1978). There is no reason to believe from the secretory studies we have performed up to 1 year after myotomy that our incidence of recurrent ulceration should be any higher. Only time will tell, for it may still be regarded as early days for highly selective vagotomy as some recurrences after posterior gastroenterostomy alone occur after over 10 years.

Early experience with gastric emptying studies has shown no evidence of either early emptying or stasis and, of course, a drainage procedure is not required. The operation carries with it all the advantages associated with preservation of the innervated pylorus, the value of which has been shown with conventional highly selective vagotomy. Hart (1968) has reported that vagal antral nerves mediate inhibition of gastric acid secretion. Dragstedt has stated that: 'Tonus and hunger contractions of the stomach in patients with duodenal ulcer are usually excessive, a temporary atony of the fundic region was observed after vagotomy. It is very likely that this reduction in hypertonicity in part accounts for the immediate symptomatic relief so commonly produced' (Dragstedt and Owens, 1943). If gastric spasm is a factor in duodenal ulcer symptoms, then, in addition to dividing vagal branches, myotomy will aid in the prevention of such contractions.

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References

AMDRUP B. M. and GRIFFITH C. A. (1969) Selective vagotomy of the parietal cell mass: part I: with preservation of the innervated antrum and pylorus. *Ann. Surg.* 170, 207–214.

AMDRUP E. and JENSEN H. E. (1970) Selective vagotomy of the parietal cell mass preserving innervation of the undrained antrum. *Gastroenterology* 59, 522–527.

AMDRUP E., JENSEN H. E., JOHNSTON D. et al. (1974) Clinical results of parietal cell vagotomy two to four years after operation. *Ann. Surg.* 180, 279–284.

BENSON C. D. and LLOYD J. R. (1964) Infantile pyloric stenosis. *Am. J. Surg.* 107, 429–433.

CARTER D. C., DOZIOS R. R. and KIRKPATRICK J. R. (1973) Gastric secretory response to insulin infusion in vagotomized subjects. *Br. J. Surg.* 60, 702–704.

DORRICOTT N. J., MCNEISH A. R., ALEXANDER-WILLIAMS J. et al. (1978) Prospective randomized multicentre trial of proximal gastric vagotomy or truncal vagotomy and antrectomy for chronic duodenal ulcer: interim results. *Br. J. Surg.* 65, 152–154.

DRAGSTEDT L. R. and OWENS F. M. JUN. (1943) Supradiaphragmatic section of the vagus nerves in treatment of duodenal ulcer. *Proc. Soc. Exp. Biol. Med.* 53, 152–159.

EMAS S. and GROSSMAN M. I. (1967) Effect of truncal vagotomy on acid and pepsin responses to histamine and gastrin in dogs. *Am. J. Physiol.* 212, 1007–1012.

GOLIGHER J. C., HILL G. L., KENNY T. E. et al. (1978) Proximal gastric vagotomy without drainage for duodenal ulcer: results after 5–8 years. *Br. J. Surg.* 65, 145–151.

GRIFFITHS C. A. and HARKINS H. N. (1957) Partial gastric vagotomy: an experimental study. *Gastroenterology* 32, 96–102.

HALL R., SUMMERS G. A. C. and GREEN M. A. (1974) Complication of proximal gastric vagotomy. *Br. Med. J.* 3, 806–807.

HALLENBECK G. A., GLEYSTEEN J. J., ALDRETE J. S. et al. (1976) Proximal gastric vagotomy: effects of two operative techniques on clinical and gastric secretory results. *Ann. Surg.* 184, 435–442.

HALVORSEN J. (1975) Ischaemic necrosis of the lesser curvature. *Br. Med. J.* 2, 590–591.

HART W. (1968) *Arch. Klin. Chir.* 322, 703.

HEADING R. C., TOTHILL P., MCLOUGHLIN G. P. et al. (1976) Gastric emptying rate measurement in man. *Gastroenterology* 71, 45–50.

HELLER E. (1913) Extramukose Cardioplastik beim chronischen Cardiospasmus mit Dilatation des Oesophagus. *Mitt. Grenzgeb. Med. Chir.* 27, 141–147.

HOLLANDER F. (1946) The insulin test for the presence of intact nerve fibres after vagal operations for peptic ulcer. *Gastroenterology* 7, 607–614.

HOLST-CHRISTENSEN J., HART-HENSON O., PEDERSON T. et al. (1977) Recurrent ulcer after proximal gastric vagotomy for duodenal and prepyloric ulcer. *Br. J. Surg.* 64, 42–46.

HUMPHREY C. S., JOHNSTON D., WALKER B. E. et al. (1972) The incidence of dumping after truncal, selective and highly selective vagotomy in men. *Br. Med. J.* 3, 785–788.

JOHNSTON D. (1975) Operative mortality and post-operative morbidity of highly selective vagotomy. *Br. Med. J.* 4, 545–547.

JOHNSTON D. and WILKINSON A. R. (1970) Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer. *Br. J. Surg.* 57, 289–296.

KENNEDY T., JOHNSTON G. W., MACRAE K. D. et al. (1975) Proximal gastric vagotomy: interim results of a randomised controlled trial. *Br. Med. J.* 2, 301–303.

KRONBORG O. and MASDEN P. (1975) A controlled randomised trial of highly selective vagotomy and pyloroplasty in the treatment of duodenal ulcer. *Gut* 16, 268–271.

LATARJET A. (1922) Resection des nerfs de l'estomac. *Bull. Acad. Méd. Paris* 97, 681–691.

LYNDON P. J., GREENALL M. J., SMITH R. B. et al. (1975) Serial insulin tests over a five-year period after highly selective vagotomy for duodenal ulcer. *Gastroenterology* 69, 1188–1195.

MCCREA E. D'ARCY (1924) The abdominal distribution of the vagus. *J. Anat. Lond.* 59, 18–40.

MITCHELL G. A. G. (1940) A macroscopic study of the nerve supply of the stomach. *J. Anat.* 75, 50–63.

NEWCOMBE J. F. (1973) Fatality after highly selective vagotomy. *Br. Med. J.* 1, 610.

STODDARD C. J., VASSILAKIS J. S. and DUTHIE H. L. (1978) Highly selective vagotomy or truncal vagotomy and pyloroplasty for chronic duodenal ulceration: a randomized, prospective clinical study. *Br. J. Surg.* 65, 793–796.

WYLLIE J. H. (1974) Complication of highly selective vagotomy. *Br. Med. J.* 2, 561.

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Antibiotic-associated colitis—a review of 66 cases

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SUMMARY

We have reviewed 66 cases of antibiotic-associated colitis since March 1975, which have been associated with a 27 per cent mortality. We believe antibiotics may predispose patients to this condition which is caused by a toxin produced by Clostridium difficile. Although the disease is rare, it is more common than previously reported. The presentation, methods of diagnosis and treatment are discussed.

PSEUDOMEMBRANOUS COLITIS was first described in the nineteenth century (Finney, 1893). In the past 30 years there has been renewed interest in the condition which has prompted many theories as to the aetiology of this disease. Initially, reports in the literature were based almost exclusively on post-mortem data. Sigmoidoscopy and rectal biopsy had rarely been performed. The bacteriological data that were analysed were usually from a swab taken at post-mortem and the culture media and bacteriological techniques were much less sophisticated than those of the present day. Penner and Druckerman (1948) reported on 9 fatal cases, 8 of whom had had an operation, and the conclusion was that 'shock' was the most important aetiological factor. However, it was argued that 'shock' was a result of the disease and not a prime cause (Dixon and Weisman, 1948).

A review of pseudomembranous colitis at the Mayo Clinic (Pettet et al., 1954) showed that there had been no increased incidence of the disease since the introduction of antibiotics. The disease was most commonly associated with operations for colonic carcinoma and it was suggested that the associated obstruction might be important.

A series of 8 cases of pseudomembranous colitis was reported in 1953 (Terplan et al., 1953) in which *Staphylococcus aureus* was identified in swabs taken from the mucosa in 5 of the patients. This observation was confirmed by many others (Speare, 1954; Hartmann and Angevine, 1956; Altemeier et al., 1963), and led to the belief that this organism was responsible for pseudomembranous colitis. However, many of the patients studied did not have a premortem stool culture and where this was performed the isolation rate of *S. aureus* was low. It was argued (Bloomfield and Waters, 1960) that the terms staphylococcal enterocolitis and pseudomembranous colitis were not synonymous but that the latter was a non-specific change to a variety of factors which might include staphylococcal enterocolitis. Furthermore, staphylococcal enterocolitis often involved the small bowel alone. Interestingly, the most successful treatment of this condition was the use of vancomycin (Wallace, 1965; Khan and Hall, 1966).

There has, however, been increasing evidence that antibiotics are a major predisposing factor for this disorder. Over 40 cases have been reported after exposure to lincomycin or clindamycin. The exact relationship of the disease to these two antibiotics is difficult to establish because they are often given in combination with other antibiotics. There have also been reports of pseudomembranous colitis being associated with other antibiotics: ampicillin (Keating et al., 1974; Simla et al., 1976); cephazolin (Fee et al., 1977); cotrimoxazole (Cameron and Thomas, 1977). In 1975 a viral aetiology was also proposed (Steer, 1975).

More recently, as a result of studies for a possible viral aetiology, a toxin was demonstrated from a patient with histologically proved pseudomembranous colitis (Larson et al., 1977). This toxin produced a characteristic cytopathic effect in cell culture which could be neutralized by *Clostridium sordelli* antitoxin. Subsequent studies in patients have demonstrated that this toxin was produced by *Clostridium difficile* (Bartlett et al., 1978; George, Symonds et al., 1978), which we now believe to be the cause of a type of pseudomembranous colitis.

We believe that the more appropriate term for the condition we have seen is antibiotic-associated colitis. The exact relationship between the presence of a faecal toxin and a pseudomembrane remains to be elucidated.

Patients and methods

We have reviewed our experience of antibiotic-associated colitis since March 1975 with respect to the method of presentation, the antibiotics prescribed, the method of diagnosis and the effect of the treatment prescribed.

In September 1977 we began routinely to screen all patients with diarrhoea for the presence of this faecal toxin using a HeLa cell culture to demonstrate this cytopathic effect (*Fig.* 1). At the same time routine bacteriology was performed for the identification of *Clostridium difficile*.

Results

We have reviewed 66 cases of antibiotic-associated colitis since March 1975. Prior to screening for the faecal toxin, we had seen 25 cases of this disease which had been diagnosed either histologically from a rectal biopsy or on post-mortem examination. Since September 1977 we have seen a further 41 cases up to February 1979, whose diagnosis was confirmed either histologically or on the presence of this faecal toxin.

Of these 66 patients, 28 were males with a mean age of 60·1 years (range 15–90); there were 38 females whose mean age was 59 years (range 29–88).

The associated disorders are reviewed in *Table I*. Fifty-six patients had one or more operations, of whom 37 (56 per cent) had disorders associated with the large bowel. Of these, 22 (33 per cent) had a carcinoma of the colon or rectum and there was evidence of obstruction in 10 patients in this group. The incidence of the disease is shown in *Fig.* 2 and there is evidence to suggest that epidemics of the disease may have occurred. This phenomenon has been reported by others (Kabins and Spira, 1975).

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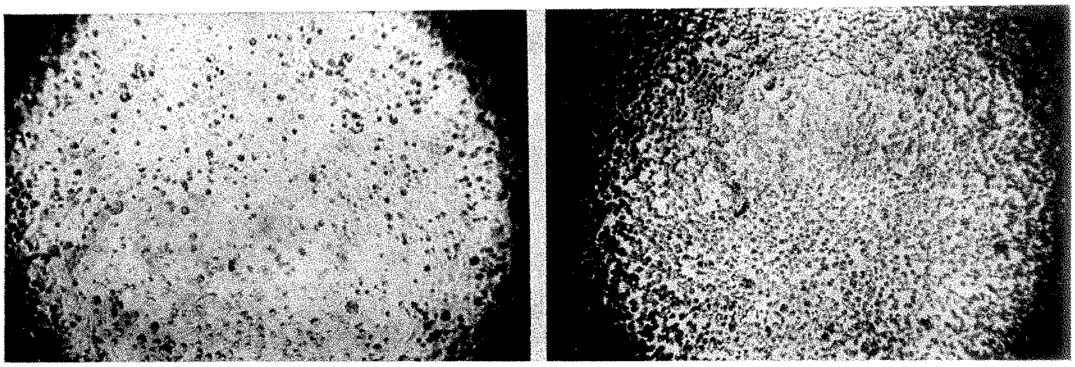
a *b*

Fig. 1. The cytopathic effect. *a*, Monolayer of HeLa cells; *b*, effect of the toxin with destruction of the monolayer and cell death.

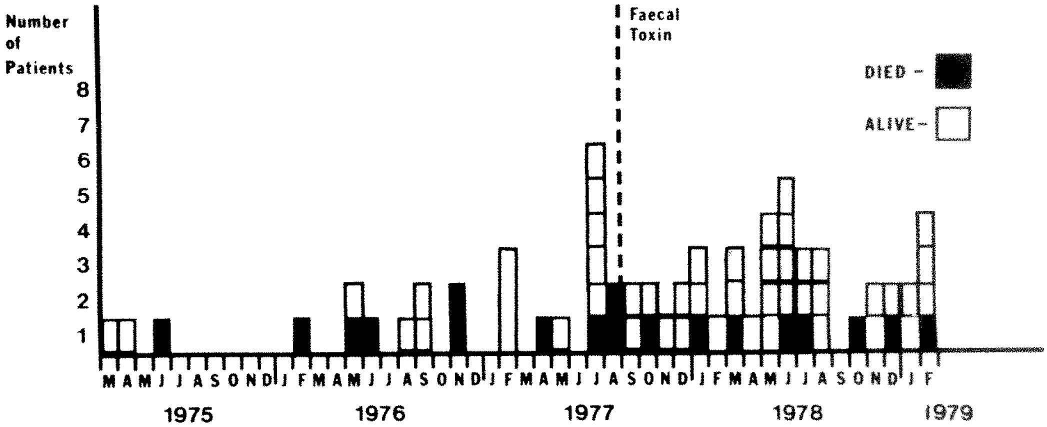

Fig. 2. The incidence of antibiotic-associated colitis 1975–9.

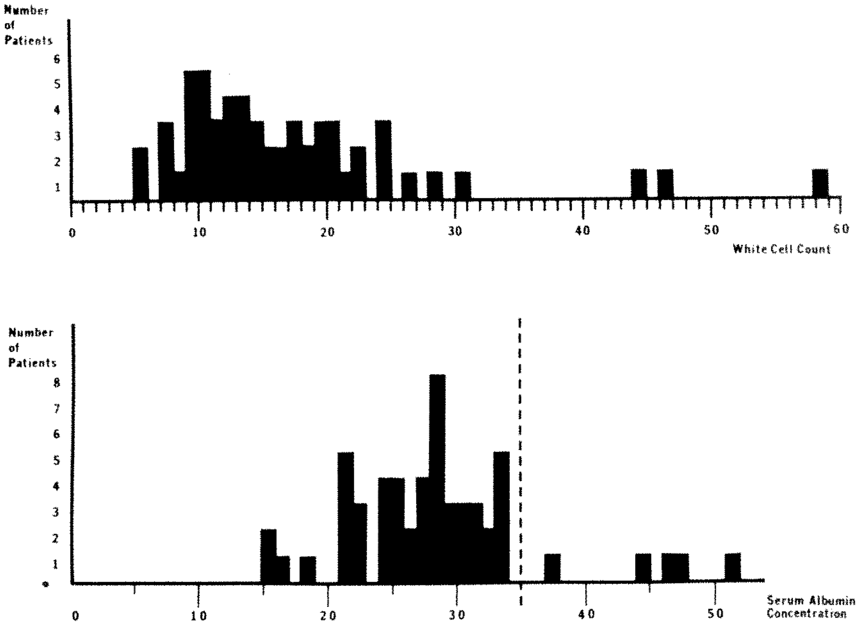

Fig. 3. Distribution of maximum white cell count ($\times 10^9$/l) ($n = 58$) and serum albumin values (g/l) ($n = 60$).

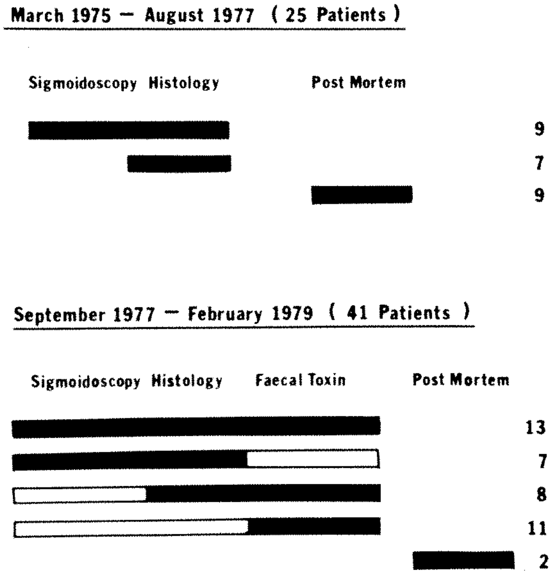

Fig. 4. Correlation between sigmoidoscopy, histology and faecal toxin.

Table I: UNDERLYING DISEASE 1975–9

Disease	No.
Large bowel (37)	
Carcinoma of colon	10
Carcinoma of rectum	12
Other	15
Small bowel (6)	
Small bowel obstruction	5
Crohn's disease	1
Gastric	4
Biliary	5
Miscellaneous	14

Table II: ANTIBIOTICS PRESCRIBED

Antibiotics	Pre-operative	Per-operative	Post-operative
Aminoglycosides	13	13	36
Lincomycin/clindamycin	2	10	30
Metronidazole	7	2	13
Ampicillin/amoxycillin	1	1	19
Cephalosporins	0	3	14
Others	2	1	38

Clinical presentation

Sixty-four patients had diarrhoea which was associated with colicky abdominal pain in 5 cases and abdominal distension with megacolon in a further 3 cases. No patient presented with either rectal bleeding or colonic perforation. The diarrhoea was usually watery but not offensive and often contained excess mucus but there was no pus or blood. The frequency of the diarrhoea was variable. The majority of patients had their bowels open between 3 and 8 times per day, but others had an even greater frequency.

Data on 60 patients showed that 40 (66 per cent) had a fever greater than 37·5 °C and of these 18 (26 per cent) had a fever of more than 38·5 °C.

Laboratory findings

Twenty-seven patients (41 per cent) had a white cell count greater than $15{\cdot}0 \times 10^9$/l (*Fig.* 3). Fifty patients (76 per cent) had a serum albumin below the lower limit of normal (*Fig.* 3) and of these, 16 (24 per cent) had a level below 25 g/l. The serum mucoproteins were estimated in only 17 patients. The mean level was 2·73 g/l with a range 0·95–5·10 g/l.

Bowel preparation and antibiotics

Bowel preparation was performed in 27 patients. Twelve patients had a whole bowel irrigation and the remaining 15 had a combination of other methods. The antibiotics prescribed were either given (*a*) preoperatively as part of the bowel preparation, (*b*) peroperatively, either with the premedication or in the anaesthetic room prior to operation, or (*c*) postoperatively, either as part of a prophylactic course or as therapy (*Table II*).

All patients had received antibiotics prior to developing the disease. A total of 205 courses of antibiotics were prescribed of which 150 (73 per cent) were given postoperatively. The groups of antibiotics prescribed reflect the nature of the surgery performed. Therefore, an aminoglycoside (most commonly gentamicin) and either lincomycin, clindamycin or more recently metronidazole were used extensively. Although some patients, especially those in the non-operated group, received a single antibiotic, many of those in the operated group received multiple courses.

Diagnosis

Prior to the introduction of screening for a faecal toxin, antibiotic-associated colitis was diagnosed histologically in 16 patients from a rectal biopsy and of these, 9 had a typical sigmoidoscopic appearance. However, the diagnosis was also made in a further 9 cases (36 per cent) only at post-mortem (*Fig.* 4).

Since September 1977, we have seen a further 41 cases. Thirteen patients (32 per cent) had sigmoidoscopic appearances of antibiotic-associated colitis which were confirmed histologically, as defined by the classification of Price and Davies (1977) and all had evidence of a faecal toxin. In 8 patients (19·5 per cent) no plaques were seen on sigmoidoscopy but there was histological and bacteriological evidence of antibiotic-associated colitis. In a further 11 patients (27 per cent) a faecal toxin only was found. However, the histology was reported as 'suspicious of antibiotic-associated colitis' or 'non-specific proctitis' in 8 patients in this group. Seven (17 per cent) patients had sigmoidoscopic and histological evidence of antibiotic-associated colitis but no faecal toxin was demonstrated. In only 2 patients was the diagnosis made at post-mortem. Barium enemas were performed on 10 patients, but the findings were not diagnostic and we no longer use this examination to establish the diagnosis. Other groups have reported similar findings (Shimkin and Link, 1973; Shapiro and Newman, 1973) though diagnostic features have been described (Sclafani et al., 1975). We have no experience with colonoscopy.

Mortality

There were 18 deaths in our series—a mortality of 27 per cent. Thirty patients were under the age of 60 years and there were 3 deaths (10 per cent) in this age group. There were 36 patients over the age of 60 and of these 15 died (41 per cent).

Treatment

Standard measures to control the diarrhoea proved ineffective. However, in a double blind trial of oral vancomycin (Keighley, Burdon et al., 1978) a rapid clinical response was reported. In the treated group there were 12 patients with *Clostridium difficile*, 9 of whom had a demonstrable faecal toxin. In the placebo group, there were 9 patients with *Clostridium difficile* of whom 7 had a faecal toxin. After 5 days of treatment with oral vancomycin in a dose of 125 mg four times a day, only one patient in the treated group still had the organism and a faecal toxin, whereas 8 patients in the placebo group still had *Clostridium difficile* and 6 still had the toxin. This reduction in the presence of toxin and the organism was accompanied by a marked improvement in the patients' symptoms.

In this series there are now 16 patients who have been treated with vancomycin. Eleven patients had a normal formed stool by the end of 5 days and the mean frequency of stools per day had fallen from 4·7 to 1·8. In the remaining 50 patients the mean duration was 15·3 days (range 4–50) with an average frequency of 6·2 stools per day (range 3–12).

Discussion

The incidence of the disease since the introduction of routine screening of all patients with diarrhoea is almost double that of the period prior to September 1977.

This may represent an actual increased incidence or alternatively an increased rate of diagnosis; we believe the latter has been the case. A number of patients develop diarrhoea especially after large bowel surgery and antibiotic therapy (Keighley, Alexander-Williams et al., 1978). This is often assumed to be 'resolution of the postoperative ileus'. Similarly, the presence of an elevated white blood count in conjunction with diarrhoea is sometimes indicative of sepsis following surgery. An elevated white blood count and diarrhoea may also occur in patients with antibiotic-associated colitis and under these circumstances the diagnosis of antibiotic-associated colitis will be missed if sigmoidoscopy and screening of faecal toxins are not performed. As a result of routinely investigating all patients who have had more than three loose stools per day or a colostomy output of greater than 1 l/day, we have diagnosed antibiotic-associated colitis in many patients in whom the disease would not previously have been suspected.

It has been suggested that we have experienced epidemics of this disease (*Fig.* 1) (June/July 1978). The reason for such outbreaks remains unresolved. An epidemiological study has failed to demonstrate a carrier state either in patients who have not previously had the disease or in the staff. However, the organism can be isolated from the faeces of children up to the age of 1 year (Hall and O'Toole, 1935). The possibility of cross-infection from infected patients or some other vector is being assessed.

The precise relationship between pseudomembranous colitis, antibiotics and the presence of toxigenic strains of *Clostridium difficile* remains to be defined. Until the pharmacology and pathogenesis of the toxin have been elucidated we believe the most appropriate term to describe the condition is antibiotic-associated colitis. This disease has been associated with many pre-existing conditions and in our series over half the cases were associated with disorders of the large bowel and a third occurred in patients with large bowel carcinoma. This, however, may only reflect the incidence of disease as seen in our gastrointestinal surgical unit.

Although antibiotic-associated colitis was considered to be specifically related to the use of lincomycin and clindamycin, we now know that other antibiotics have been implicated in patients developing the disease. Even short courses of antibiotics for prophylaxis have been shown to be responsible. Many of these antibiotics have been used in combinations which are known to exert an influence on the bacterial flora of the gastrointestinal tract. In a recent study (Keighley et al., 1979) it was shown that antibiotics which did not influence the microflora of the colon were not accompanied by antibiotic-associated colitis. These findings support the hypothesis that antibiotic-associated colitis may be due to an overgrowth of an organism normally present in small numbers within the colon.

Since September 1977, the diagnosis of antibiotic-associated colitis has only been confirmed sigmoidoscopically in 49 per cent of cases and histologically in 68 per cent. There are a number of factors which may explain the discrepancy between these results and the demonstration of a faecal toxin in 32 of our 41 patients (78 per cent). Careful sigmoidoscopy is required to identify the characteristic plaques as these may be obscured either by faecal fluid or by mucus adherent to the bowel wall. Gentle removal of this mucus is required otherwise the plaques may be dislodged, especially if the tip of the sigmoidoscope is used for this purpose. Secondly, if the biopsy does not incorporate a plaque, or more preferably a plaque/mucosa junction, the histological interpretation may be very difficult. Thirdly, repeat sigmoidoscopy is often required, possibly daily, before the classic morphological features are seen. There is a suggestion that the titre of faecal toxin is higher in patients with histologically proved disease than in those with 'non-specific' findings (Burdon, 1979). Finally, rectal sparing has been demonstrated at post-mortem examination. Although the presence of *Clostridium difficile* is not diagnostic of antibiotic-associated colitis we have isolated the organism in almost 90 per cent of our last 41 cases.

Treatment with vancomycin has proved an effective method of eradicating both the *Clostridium difficile* and its toxin; furthermore, vancomycin has been associated with a marked symptomatic improvement. General methods of treatment such as codeine phosphate and Lomotil (Searle) have proved ineffective. Indeed, the latter has possibly been associated with the development of toxic megacolon (Gibson et al., 1975). The demonstration that certain resins absorb the toxin (George, Symonds et al., 1978) offers possible treatment without the further use of antibiotics, which is appealing. In a recent study using cholestyramine (Kreutzer and Milligan, 1978) in a dose of 4 g/day, a good response was obtained in 12 patients with histologically proved disease.

References

ALTEMEIER W. A., HUMMEL R. P. and HILL E. O. (1963) Staphylococcal enterocolitis following antibiotic therapy. *Ann. Surg.* **157**, 847–858.

BARTLETT J. G., CHANG T. W., GURWITH M. et al. (1978) Antibiotic-associated pseudomembranous colitis due to a toxin producing clostridia. *N. Engl. J. Med.* **298**, 531–534.

BLOOMFIELD D. A. and WATERS M. N. I. (1960) Pseudomembranous enterocolitis. *Med. J. Aust.* **2**, 854–857.

BURDON D. W. (1979) Personal communication.

CAMERON A. and THOMAS M. (1977) Pseudomembranous colitis and co-trimoxazole. *Br. Med. J.* **1**, 1321.

DIXON C. F. and WEISMANN R. E. (1948) Acute pseudomembranous enterocolitis and antibiotics: a complication following intestinal surgery. *Surg. Clin. North Am.* **28**, 999–1023.

FEE H. J., AMENT M. E. and HOLMES E. C. (1977) Pseudomembranous colitis associated with cephazolin therapy. *Am. J. Surg.* **133**, 237–248.

FINNEY J. M. T. (1893) Gastroenterostomy for a cicatrising ulcer of the pylorus. *Bull. Johns Hopkins Hosp.* **4**, 53.

GEORGE R. H., SYMONDS J. M., DIMOCK F. et al. (1978) Identification of *Clostridium difficile* as a cause of pseudomembranous colitis. *Br. Med. J.* **1**, 695–697.

GEORGE R. H., YOUNGS D. J., JOHNSON E. M. et al. (1978) Anion-exchange resins in pseudomembranous colitis. *Lancet* **2**, 624.

GIBSON G. E., ROWLAND R. and HECKER R. (1975) Diarrhoea and colitis associated with antibiotic treatment. *Aust. NZ J. Med.* **5**, 340–347.

HALL I. C. and O'TOOLE E. (1935) Intestinal flora in the newborn infant. *Am. J. Dis. Child.* **40**, 390–402.

HARTMANN H. A. and ANGEVINE D. M. (1956) Pseudomembranous colitis complicating prolonged antibiotic therapy. *Am. J. Med. Sci.* **232**, 667–673.

KABINS S. A. and SPIRA T. J. (1975) Outbreak of clindamycin associated colitis. *Ann. Intern. Med.* **83**, 830.

KEATING J. P., FRANK A. L., BARTON L. L. et al. (1974) Pseudomembranous colitis associated with ampicillin therapy. *Am. J. Dis. Child.* **128**, 369–370.

KEIGHLEY M. R. B., ALEXANDER-WILLIAMS J., ARABI Y. et al. Diarrhoea and pseudomembranous colitis after gastrointestinal operations. *Lancet* **2**, 1165–1168.

KEIGHLEY M. R. B., BURDON D. W., ARABI Y. et al. (1978) Randomised controlled trial of vancomycin for pseudomembranous colitis and post-operative diarrhoea. *Br. Med. J.* **2**, 1667–1669.

KEIGHLEY M. R. B., ARABI I., ALEXANDER-WILLIAMS J. et al. (1979) A comparison between systemic and oral antimicrobial prophylaxis in colorectal surgery. *Lancet.* (In the press.)

KHAN M. Y. and HALL W. H. (1966) Staphylococcal enterocolitis treatment with oral vancomycin. *Ann. Intern. Med.* **65**, 1–8.

KREUTZER E. W. and MILLIGAN F. D. (1978) Treatment of antibiotic associated pseudomembranous colitis with cholestyramine resin. *Johns Hopkins Med. J.* **143**, 67–72.

LARSON H. E., PARRY J. V., PRICE A. B. et al. (1977) Undescribed toxin in pseudomembranous colitis. *Br. Med. J.* **1**, 1246–1248.

PENNER A. and DRUCKERMAN L. J. (1948) Enterocolitis as a post-operative complication and its significance. *Gastroenterology* **11**, 479–487.

PETTET J. D., BAGGENSTOSS A. H., DEARING W. et al. (1954) Post-operative pseudomembranous enterocolitis. *Surg. Gynecol. Obstet.* **98**, 546–552.

PRICE A. B. and DAVIES D. R. (1977) Pseudomembranous colitis. *J. Clin. Pathol.* **30**, 1–12.

SCLAFANI S. J. A., DALLEMAND S. E., SUTTON A. et al. (1975) Radiopathologic correlation in pseudomembranous colitis. *Dis. Colon Rectum* **18**, 694–698.

SHAPIRO R. L. and NEWMAN A. (1973) Acute enterocolitis. *Diag. Radiol.* **108**, 263–268.

SHIMKIN P. M. and LINK P. J. (1973) PMC: a consideration in the barium enema differential diagnosis of acute generalised ulcerative colitis. *Br. J. Radiol.* **46**, 437–439.

SIMLA S., KOUVALAINEN K. and MAKELA P. (1976) Pseudomembranous colitis after amoxycillin. *Lancet* **2**, 317–318.

SPEARE G. S. (1954) Staphylococcal pseudomembranous enterocolitis—a complication of antibiotic therapy. *Am. J. Surg.* **88**, 523–534.

STEER H. W. (1975) PMC associated with clindamycin therapy: a viral aetiology. *Gut* **16**, 695–706.

TERPLAN K., PAINE J. R., SHEFFER J. et al. (1953) Fulminating gastroenterocolitis caused by staphylococci. *Gastroenterology* **24**, 476–503.

WALLACE J. F. (1965) Oral vancomycin treatment of staphylococcal enterocolitis. *N. Engl. J. Med.* **272**, 1014–1015.

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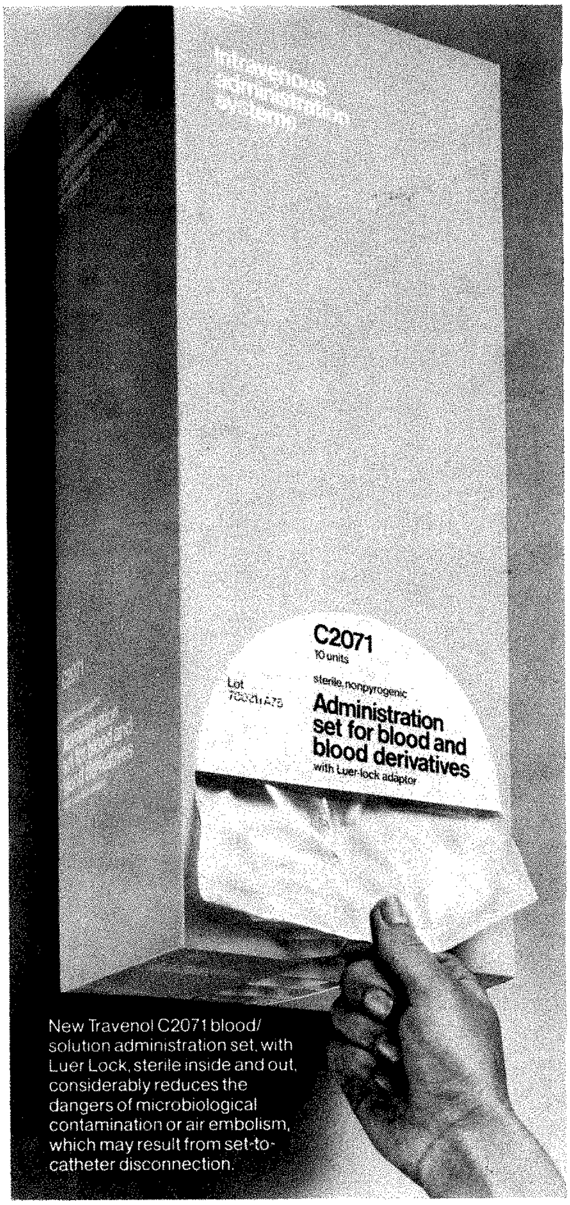
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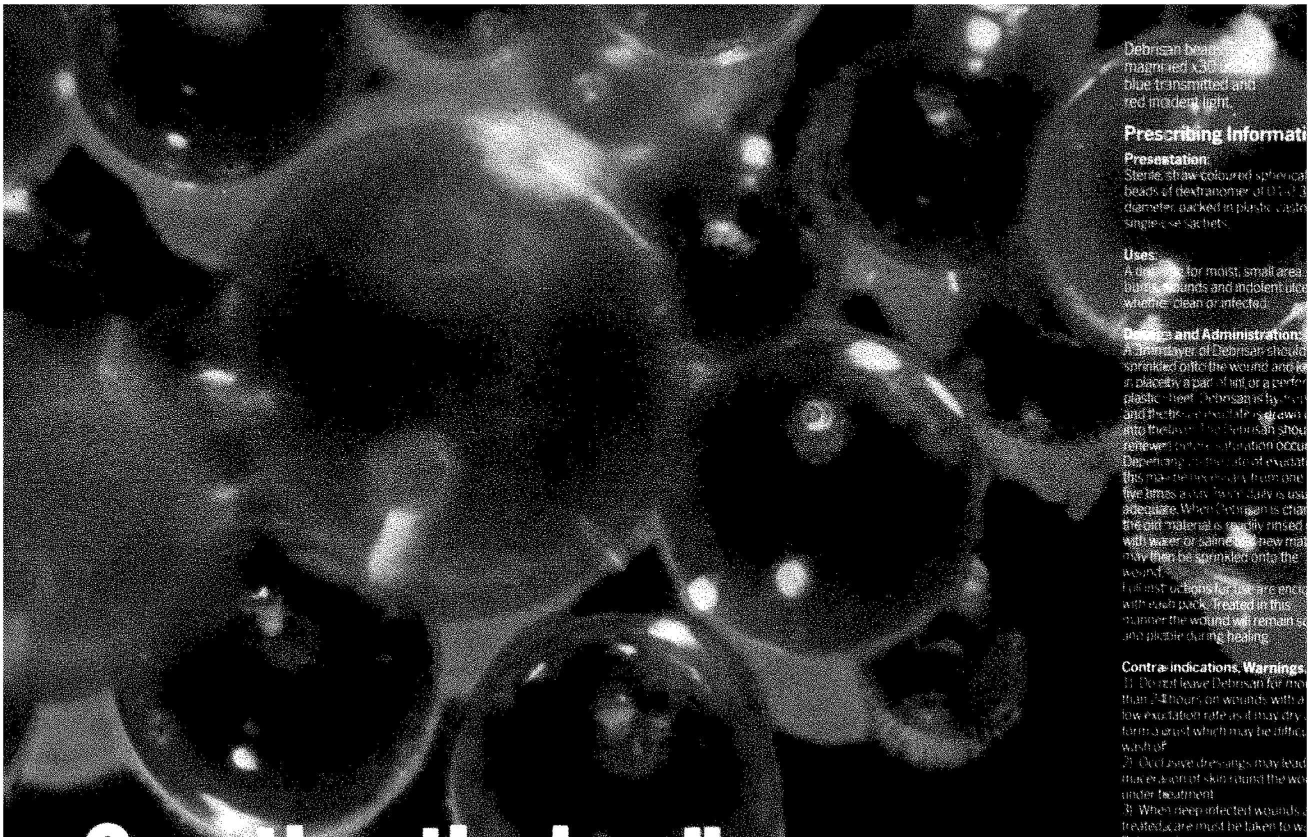Debrisan beads
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in place by a pad of lint or a perfo
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adequate. When Debrisan is chan
the old material is readily rinsed
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under treatment.
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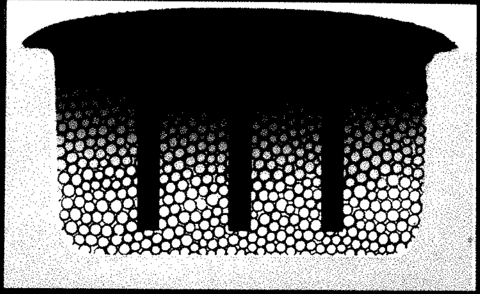

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Br. J. Surg. Vol. 66 (1979) 743–748

Anorectal Crohn's disease

N. S. WILLIAMS, J. MACFIE AND L. R. CELESTIN*

SUMMARY

Four hundred and twenty-three patients with Crohn's disease have been reviewed, 48 of whom had isolated anorectal involvement—an incidence of 11·4 per cent. These patients were compared with 48 randomly selected and sex-matched cases who presented with isolated ileocolic disease.

The age of the anorectal patients (53·6 ± 18 years) was greater than that of the controls (34·2 ± 12 years). The duration of follow-up was 6·0 ± 4 years and 12·6 ± 8 years respectively. Rectal bleeding, diarrhoea and perianal disease were more common in the anorectal group. Twenty-two patients (46 per cent) with anorectal disease and 40 (83 per cent) in the ileocolic group underwent definitive surgery. There were 4 (18 per cent) postoperative deaths in the anorectal group and none among the controls.

The incidence of recurrence was lower among the anorectal patients (21 per cent) compared with the ileocolic group (40 per cent). However, the estimated probability of recurrence, based on the duration of follow-up, the number of deaths during follow-up and the actual incidence of recurrence, is similar in both groups.

CROHN's disease may be confined to the rectum and anal canal with no evidence of disease elsewhere in the gastrointestinal tract. This variant of the disease has been termed anorectal Crohn's disease (*British Medical Journal*, 1976), and until recently there was little information available about it. Farmer et al. (1975) analysed the case records of 615 patients with Crohn's disease who presented to the Cleveland Clinic between 1966 and 1973. They found 21 patients (3·4 per cent) who presented initially with the disease localized to the anorectum but failed to give any detailed account of their clinical course. A more comprehensive review of this disease entity came from Ritchie and Lennard-Jones (1976) of St Mark's Hospital. These authors reviewed 80 patients with anorectal disease seen between 1940 and 1974. They concluded that anorectal Crohn's disease should be considered as a well-defined variant of the disease as it has a better prognosis and the mortality rate is low whatever treatment is employed. Furthermore, in contradistinction to Crohn's disease at other sites, recurrence or proximal spread after surgery is uncommon, so that surgery often results in cure.

As the management of Crohn's disease varies widely between different centres and results are assessed differently, we decided to review our own cases in the light of these recent articles.

Patients and methods

The case records of 423 patients with Crohn's disease treated at the General Infirmary, Leeds, and at Frenchay Hospital, Bristol, between 1939 and 1977 have been reviewed. Forty-eight patients presented with disease confined to the anorectal region—an incidence of 11·4 per cent.

The diagnosis was established by histological, sigmoidoscopic and radiological criteria. Although all patients did not have typical histological features of Crohn's disease, the radiological and sigmoidoscopic changes were considered to be compatible with Crohn's proctitis as defined by the following criteria.

Proctosigmoidoscopic features

Anal canal and perianal region: Demonstration of ulceration, fistulas, fissures, fleshy, oedematous skin tags or stricture of the anal canal.

Rectal mucosa: Evidence of inflammatory change, including mucosal oedema, friability and 'cobblestoning' of the mucosa. The presence of discrete ulcers, linear ulcers resembling fissures or areas of inflamed mucosa adjacent to normal mucosa (*Fig*. 1).

Radiological features

Evidence of rectal disease with or without distal sigmoid involvement, demonstrated by loss of mucosal pattern with 'cobblestone' mucosal changes, longitudinal or rake ulceration, fissuring and segmental involvement (Marshak and Lindner, 1967) (*Fig*. 2).

The diagnosis of anorectal Crohn's disease was only made if the disease was confined to the rectum and lower sigmoid colon with or without anal involvement. All cases included in the series were proved to have absence of disease elsewhere in the gastrointestinal tract either on radiological investigation, including small bowel meal, or on evidence from laparotomy. If the disease extended proximal to the left iliac crest on barium enema or was isolated to the perianal region or sigmoid colon alone, with no evidence of rectal involvement, the patient was excluded from the series.

As it has been previously suggested that anorectal Crohn's disease runs a more benign course and exhibits different clinical features from the more common ileocolic variety, we decided to compare our cases with 48 patients who presented initially with isolated ileocolic disease. These patients were randomly selected and matched for sex.

Results

We would point out that although statistically significant differences can be demonstrated between the two groups, these have not been quoted, as the two disease types cannot be considered to arise from the same population.

Age and sex: The mean age in the anorectal group was 54·7 years (range 17–77) and 35·4 years (range 15–71) in the ileocolic group (*Fig*. 3). There were 18 males and 36 females in both groups.

Histology: Typical histological features were noted in 28 patients (58 per cent) presenting with anorectal involvement and in 33 (69 per cent) with ileocolic disease. Non-specific inflammatory changes were demonstrated in the remaining patients in both groups.

Follow-up: The mean duration of follow-up was 6·1 years and 12·3 years respectively. In 7 patients of the anorectal group and in 5 of the ileocolic group follow-up was incomplete.

Clinical features: These are summarized in *Table I*. As would be expected, diarrhoea and rectal bleeding were more common in patients with involvement of the distal colon. Of the 27 patients with perianal disease in the anorectal group, 12 had presented

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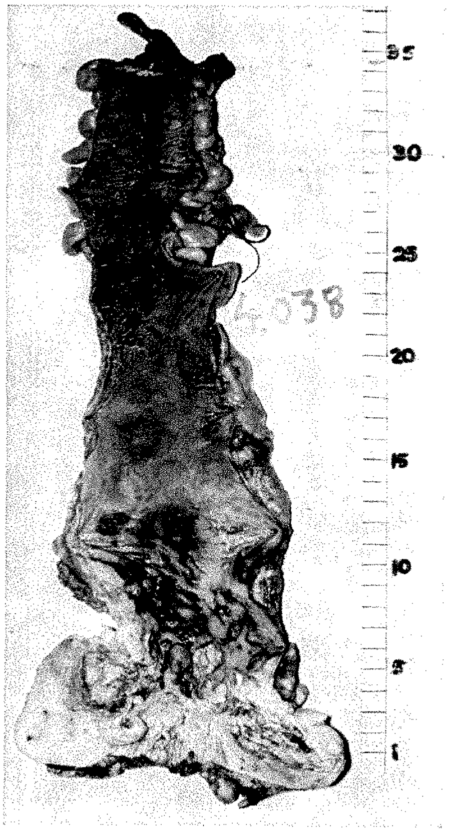

Fig. 1. Rectal excision specimen of a patient with anorectal Crohn's disease.

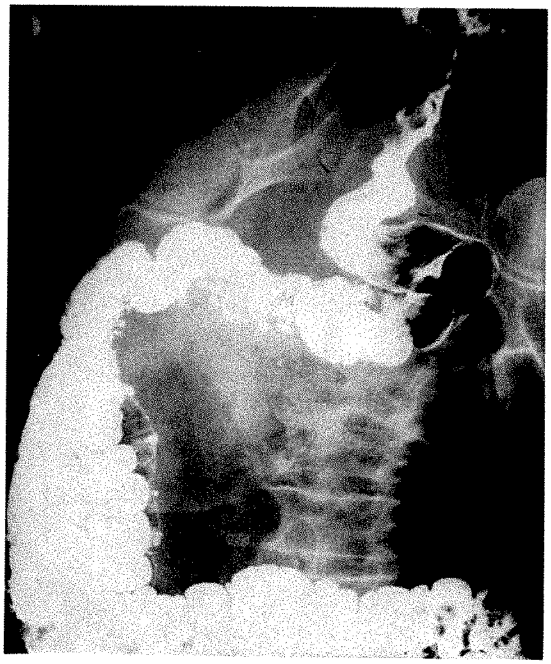

Fig. 2. Double-contrast barium enema illustrating Crohn's involvement of the rectum and a normal remaining colon.

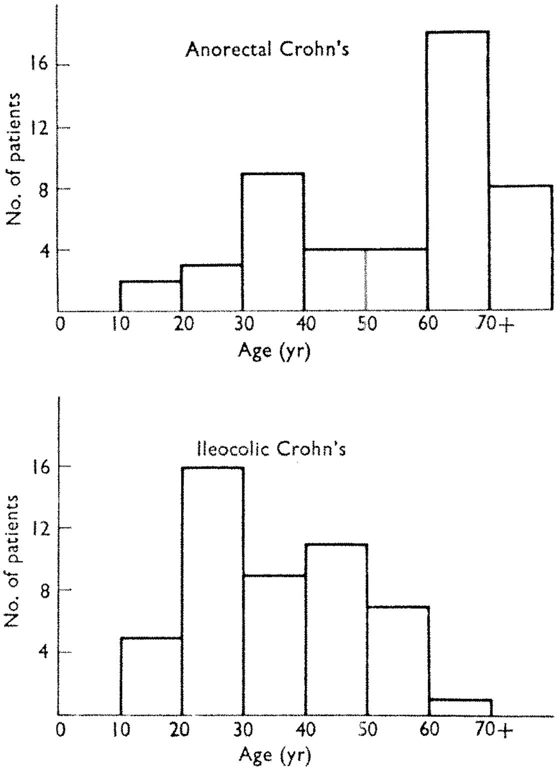

Fig. 3. Distribution of age at presentation.

Table I: CLINICAL FEATURES

	Anorectal	Ileocolic
Diarrhoea	37 (79%)	28 (58%)
Rectal bleeding	31 (66%)	4 (8%)
Associated perianal disease	27 (57%)	5 (10%)
Weight loss	17 (36%)	14 (29%)
Abdominal pain	16 (34%)	38 (79%)
Anaemia	13 (28%)	20 (42%
Rectal stricture	6 (13%)	0
Abdominal mass	0	10 (21%)
Obstruction	0	13 (27%)
Associated conditions	8 (16%)	4 (8%)

Table II: CONSERVATIVE TREATMENT

	Anorectal	Ileocolic
Total no.	37 (77%)*	13 (27%)*
Steroids	34	8
Salazopyrin	20	2
Azathioprine	5	0
Other	5	4

* Percentage of 48 cases.

several months or years before the diagnosis of Crohn's disease was established. The major complaint in 6 patients with ano-rectal disease was of intractable constipation, subsequently shown to be due to a rectal stricture. Associated symptoms included 7 patients with polyarthritis and 1 with erythema nodosum in the anorectal group compared with 3 cases of polyarthritis and 1 of irridocyclitis in the ileocolic group.

It should be noted that 7 of the 48 patients with anorectal disease had concomitant involvement of the distal sigmoid.

Treatment

Conservative (*Table II*): Drug therapy was the initial treatment in 37 of the anorectal group and 13 of the ileocolic group. The numbers of patients listed in *Table II* refer to drug therapy prescribed on presentation only. Steroid therapy involved systemic steroids in both groups. Topical steroids were commonly prescribed in the anorectal group but patients are not listed in *Table II* unless they also received systemic therapy. Salazopyrin was prescribed in 20 patients with anorectal disease, 15 of whom had concomitant steroid therapy.

Surgery: Twenty-two patients (46 per cent) with anorectal disease and 40 (83 per cent) with ileocolic disease underwent definitive surgery.

Indications (*Table III*): The most common indications for surgery in the anorectal group were rectal bleeding (64 per cent), persistent diarrhoea with mucopus (36 per cent) and intractable constipation as a result of rectal stricturing (27 per cent). Abdominal pain (48 per cent), intestinal obstruction (33 per cent) and diarrhoea (30 per cent) were the most frequent indications for surgery in patients with ileocolic disease.

Results of surgery: The surgical procedures performed and the results of surgery are shown in *Table IV*.

Operative mortality: There were 3 postoperative deaths in the anorectal group and none in the ileocolic. There was one further death in the anorectal group in a patient undergoing further surgery for recurrence.

Subsequent surgery: The numbers of patients who required further definitive surgery for Crohn's disease are shown in *Table IV*. It should be emphasized that not all patients were reoperated upon for recurrent disease.

Anorectal group: Of 7 patients who initially underwent a bypass procedure (defunctioning colostomy or ileostomy) 1 died and 5 required further surgery, of whom 3 had proved recurrence. Fifteen patients had a primary resection and the operative procedures are shown. There were 2 postoperative deaths and only 2 patients required further surgery, both of whom had previously had a rectal excision.

Ileocolic group: Of 23 patients who initially had a bypass, exploration or appendicectomy alone, 12 required further surgery. Only 5 of these cases had proved recurrence, the remainder undergoing surgery for excision of their original lesion. Seventeen patients had a primary excision, 9 of whom required further surgery, all for recurrence.

Recurrence

Patients with continuing symptoms or patients in whom a bypass procedure was performed initially have not been included in the analysis of recurrence unless there was definite evidence that the disease process involved a different site from that on presentation.

Ten patients (21 per cent) with anorectal disease and 19 (40 per cent) with ileocolic disease had proved recurrence. The mean time interval between initial diagnosis of the Crohn's disease and the confirmation of recurrence was 5·7 years and 5·8 years respectively. *Fig.* 4 shows the estimated probability of recurrence based on life table calculations (Berkman and Gage, 1950).

Table III: INDICATIONS FOR SURGERY

	Anorectal (*n* = 22)	Ileocolic (*n* = 40)
Rectal bleeding	14 (64%)	0
Persistent diarrhoea	8 (36%)	12 (30%)
Rectal stricture	6 (27%)	0
Suspected malignancy	2 (9%)	0
Abdominal pain	0	19 (48%)
Intestinal obstruction	0	13 (33%)
Abdominal mass	0	7 (17%)
Other	2 (9%)	14 (35%)

Table IV: RESULTS OF SURGERY

	No. of patients	Operative mortality	Subsequent surgery	Recurrence
Anorectal				
Proctocolectomy	5	1	0	0
Abdominoperineal excision of rectum	7	0	2	3*
Anterior resection	3	1	0	0
Defunctioning ileostomy	1	0	0	0
Defunctioning colostomy	6	1	5	3†
Total	22 (46%)‡	3	7	6
Ileocolic				
Right hemicolectomy	14		7	7
Small bowel resection	2		1	1
Subtotal colectomy	1		1	1
Ileotransverse bypass	18		9	5
Exploration alone	3		2	2
Appendicectomy	2		1	2
Total	40 (83 %)‡	0	21	18

* All colon.
† 1 ileum and colon; 2 colon. 1 further postoperative death.
‡ Percentages of 48 cases.
All figures are numbers of patients.

Table V: SITE OF RECURRENCE

	Anorectal	Ileocolic
No. of patients	10	19
Site		
Ileum	2	25
Colon and ileum	1	4
Colon alone	9	0
Rectum	—	1
Duodenum	0	2
Total no. of episodes	12	32

Table VI: TREATMENT OF RECURRENCE

	Anorectal	Ileocolic
Medical	4	5
Surgical	8	27
	12*	32
Surgery of recurrence		
Proctocolectomy	4	1
Right hemicolectomy	1	6
Subtotal colectomy	1	2
Left hemicolectomy	2	1
Abdominoperineal excision of rectum		1
Small bowel resection		4
Bypass		3
Total	8	18 9 unknown

* Total episodes of recurrence.

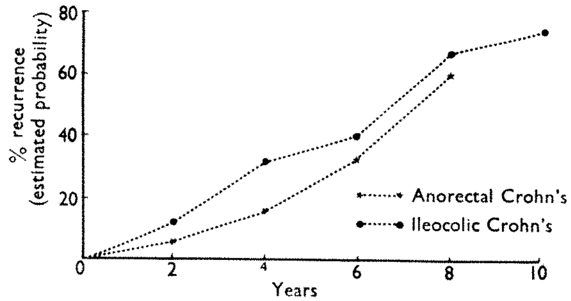

Fig. 4. Estimated probability of recurrence plotted against time. (Based on life table calculations adopted from Berkman and Gage, 1950.)

The probability of recurrence is similar in both groups despite the finding that there is a difference in actual incidences. This apparent discrepancy is explained by the large difference in the numbers of deaths that occurred during follow-up in the respective groups (anorectal 11; ileocolic 3).

Site: *Table V* illustrates the frequency of recurrence at various sites in the gastrointestinal tract as well as the total number of episodes of recurrence in the two groups. In the majority of patients with anorectal disease the recurrence was within the large bowel. Conversely, in most patients presenting with ileocolic disease who showed recurrence, this was in the ileum.

Treatment of recurrence: Table VI summarizes the treatment of recurrent disease. All the patients with anorectal disease who underwent surgery for recurrence required further colonic resection.

Discussion

It is commonly stated that in about 50 per cent of patients with Crohn's disease of the large bowel the rectum is not involved (Goligher, 1975). Indeed, many clinicians regard rectal 'sparing' as an important clinical feature in distinguishing between Crohn's disease and ulcerative colitis. That the rectum may be involved with no evidence of disease elsewhere has only recently been appreciated (*British Medical Journal*, 1976). Since the information regarding this variant of the disease is sparse, it is difficult to know its true incidence, but it would seem to be low—about 4 per cent according to Farmer et al. (1975). An incidence of over 11 per cent in our series is therefore surprising. Since Leeds General Infirmary has a particular interest in large bowel surgery it was thought that this might predjudice the results. However, this has not been found to be the case, since the incidence of the disease in the cases from Bristol, where this bias does not apply, is the same.

Diagnosis of this distal form of Crohn's disease and its differentiation from non-specific proctitis or distal ulcerative colitis may be difficult. The finding of typical histology (Hadfield, 1939; Lockhart-Mummery and Morson, 1960, 1964) on biopsy is conclusive evidence but, often, one has to rely on clinical, radiological and sigmoidoscopic evidence. This difficulty is represented in our series, as only 58 per cent of the anorectal patients had characteristic histological findings. It must be emphasized, however, that the remaining patients were only included in the series if they fulfilled the strict diagnostic criteria previously described.

There is little doubt that patients with anorectal disease present in a different way from patients with ileocolic disease. The patients with anorectal disease are older, the majority (62 per cent) being over 50 years of age (*Fig.* 1). The most common presenting symptoms were, as expected, rectal bleeding and diarrhoea (*Table I*). Not surprisingly, abdominal pain and intestinal obstruction with or without an abdominal mass were common clinical features in the patients with ileocolic disease. Perianal disease occurred more frequently in the anorectal group and this finding is compatible with results from other authors who have shown that the more distal the disease, the greater the incidence of perianal lesions (Morson and Lockhart-Mummery, 1959; Fielding, 1972). An incidence of 57 per cent, however, does not confirm the statement of Lockhart-Mummery (1972) that when the rectum itself is involved the incidence of these lesions is nearly 100 per cent. It is well known that perianal involvement may precede the onset of intestinal disease, and indeed for some time may be the only manifestation of the disease. Our findings do not differ in this respect, as 12 of our patients presented initially with perianal disease several months to years before the rectal involvement declared itself.

Crohn's disease situated anywhere in the gastrointestinal tract may produce stricture formation. The rectum does not appear to be an exception, as 6 patients presented with intractable constipation subsequently confirmed to be due to a Crohn's stricture. Two further patients in the anorectal group who presented with rectal bleeding and the passage of mucopus were diagnosed as cases of rectal carcinoma. In both cases perianal disease was absent, sigmoidoscopy and barium enema examination were suspicious of carcinoma but preoperative biopsy was inconclusive. The correct diagnosis was finally confirmed after section of the surgical specimen. This emphasizes the importance of taking multiple biopsies in all patients with a rectal stricture.

The same spectrum of associated conditions occurs in anorectal disease as in the ileocolic variety, although arthritis is more common. This may be related to the older age of the anorectal patients, but it is interesting to note that Greenstein et al. (1976) found arthritis to be the most common complication of Crohn's colitis.

Drug therapy for Crohn's disease is difficult to rationalize as there have been few controlled prospective therapeutic trials. We believe, however, that the simplest drugs available to control symptoms should be employed. Therefore the policy in both units for treating this distal form of the disease is a conservative one, using local steroid preparations with or without Salazopyrin in the first instance. Systemic steroids are used if these measures fail or if the disease causes general ill health. Azathioprine is reserved for use only in those cases failing to respond to the previous measures.

It will be appreciated that it is difficult to draw any firm conclusions about differences in drug therapy in any retrospective study as one is never completely sure about the completeness of the data. However, it should be noted that a total of 34 patients (71 per cent) with anorectal disease required either oral steroids or azathioprine in comparison to 8 patients (17 per cent) in the ileocolic group (*Table II*). This suggests that symptoms were more severe in our patients than in

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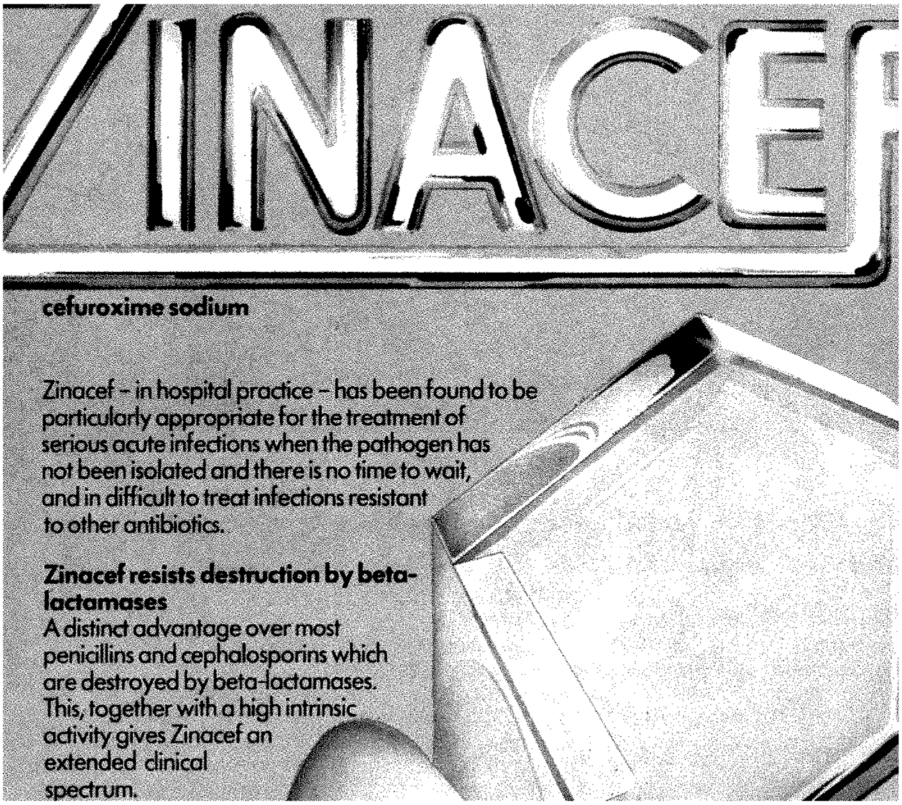

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the 80 patients reported from St Mark's Hospital (Ritchie and Lennard-Jones, 1976), where only 22 patients (27 per cent) required these drugs.

There is little information in the literature concerning the surgical management of this variety of the disease. Ritchie and Lockhart-Mummery (1973) reported on 26 patients treated surgically. A defunctioning colostomy was performed in 7 of these patients but proved ineffective in controlling symptoms. The remaining patients were treated successfully by abdominoperineal resection of the rectum with no operative mortality. As can be seen from *Table IV*, 22 patients (46 per cent) in our series required surgery as compared with 40 (83 per cent) in the ileocolic group. The indications for surgery in the anorectal patients are summarized in *Table III*, the most common being severe rectal bleeding. Four patients (18 per cent) in the anorectal group died in the postoperative period, 3 following the initial surgical procedure and 1 following a second operation for recurrence. There were no operative deaths in the ileocolic group despite the greater number operated on. Perhaps this difference reflects the greater age of the patients with anorectal disease.

It is generally accepted that excision is the best form of surgical treatment for Crohn's disease of the colon. In 1968 Oberhelman et al. recommended, as an alternative, temporary exclusion of the entire large bowel by means of an ileostomy. These authors claimed that, unlike ulcerative colitis, the disease became quiescent when the diseased segment was excluded. Several other workers (Jones et al., 1966; Burman et al., 1971; McIlrath, 1971), however, have found the long term results of bypass surgery to be unsatisfactory. As regards anorectal disease, our findings support an aggressive approach. Of the 7 patients submitted to a defunctioning procedure as the primary procedure, 5 required rectal excision at a later date. This contrasts sharply with the 15 patients who underwent excision in the first instance, only 2 of whom required a second operation.

The question inevitably arises as to how extensive the excision should be in patients with this variety of the disease. In dealing with Crohn's disease of the small bowel most experienced surgeons remove 20–25 cm of healthy bowel both proximal and distal to the diseased segment. As far as anorectal disease is concerned, the problem is whether to perform an abdominoperineal resection of the rectum or a proctocolectomy. Unfortunately, the number of patients in our series is too small to make any recommendations. It is interesting, however, that of the 7 patients who underwent abdominoperineal resection initially, 3 developed recurrence in the remaining colon, whereas of the 4 patients surviving proctocolectomy, none developed recurrence.

When discussing recurrence it is essential to define what one means. Contrary to some authors (Lennard-Jones and Stalder, 1966), we have not accepted a relapse of symptoms as indicating recurrence, unless it was accompanied by firm supporting evidence of further disease, usually from laparotomy but sometimes from radiological study. Also, following a bypass or defunctioning procedure, we do not regard disease remaining in the defunctioned segment as a recurrence, preferring to use this term only when disease has been found elsewhere. With regard to these stipulations, 10 patients in the anorectal group showed recurrence, compared with 19 in the control group. We believe that this may not reflect a true difference between the two groups mainly because the mean follow-up period is much shorter in the anorectal group. Indeed, if the estimated probability of recurrence is calculated for the two groups, it appears that after 8 years the number of patients suffering recurrence may become equal (*Fig.* 3).

Our results confirm that anorectal Crohn's disease does present in a manner different from ileocolic disease. It occurs in an older age group and presents with different clinical features. Whether or not it can be considered as a more benign variant of the disease, however, is debatable. Although 54 per cent of our patients avoided surgery, the majority required potentially toxic drugs to keep the disease in remission. When surgery was required this was often of a major nature performed in elderly patients and this is reflected in the higher operative mortality rate. Furthermore, these patients have an incidence of recurrence of 21 per cent which may increase with an extension of follow-up to approach that of ileocolic disease.

In conclusion, we would suggest that Crohn's disease is a single disease entity, albeit with certain definable patterns of presentation depending on the site of involvement, and anorectal Crohn's is one example of this. Given sufficient time, however, the disease will behave in a similar manner irrespective of where it initially develops.

Acknowledgements

We would like to thank Professor D. Johnston and Mr G. L. Hill for their help and encouragement and Mrs E. Nutter for secretarial assistance.

References

BERKMAN J. and GAGE R. P. (1950) Calculation of survival rates. *Proc. Staff Meetings Mayo Clin.* **25**, 270–286.

BRITISH MEDICAL JOURNAL (1976) Anorectal Crohn's disease. **2**, 1341.

BURMAN J. H., WILLIAMS J. A., THOMPSON H. et al. (1971) The effect of diversion of the intestinal content on the progress of Crohn's disease of the large bowel. *Gut* **12**, 11–17.

FARMER R. G., HAWK W. A. and TURNBULL R. B. JUN. (1975) Clinical patterns in Crohn's disease: a statistical study of 615 cases. *Gastroenterology* **68**, 627–635.

FIELDING J. K. (1972) Perianal lesions in Crohn's disease. *J. R. Coll. Surg. Edinb.* **17**, 32–37.

GOLIGHER J. C. (1975) *Surgery of the Anus, Rectum and Colon*, 3rd ed. London, Baillière Tindall, p. 1020.

GREENSTEIN A. J., JANOWITZ H. D. and SACHAS D. B. (1976) The extra intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine (Baltimore)* **55**, 401–403.

HADFIELD G. (1939) The primary histological lesion of regional ileitis. *Lancet* **2**, 773–775.

JONES J. H., LENNARD-JONES J. E. and LOCKHART-MUMMERY H. E. (1966) Experience in the treatment of Crohn's disease of the large intestine. *Gut* **7**, 448–456.

LENNARD-JONES J. E. and STALDER G. A. (1967) Prognosis after resection of chronic regional ileitis. *Gut* **8**, 332.

LOCKHART-MUMMERY H. E. (1972) Anal lesions of Crohn's disease. *Clin. Gastroenterol.* **1**, 377–391.

LOCKHART-MUMMERY H. E. and MORSON B. C. (1960) Crohn's disease (regional enteritis) of the large intestine and its distinction from ulcerative colitis. *Gut* **1**, 87–105.

LOCKHART-MUMMERY H. E. and MORSON B. C. (1964) Crohn's disease of the large intestine. *Gut* **5**, 493–509.

MCILRATH D. C. (1971) Diverting ileostomy or colostomy in the management of Crohn's disease of the colon. *Arch. Surg.* **103**, 308–312.

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Is the investigation of patients with breast cancer for occult metastatic disease worth while?

A. P. M. FORREST, ELIZABETH L. M. CANT, M. MAUREEN ROBERTS, HELEN J. STEWART, M. D. SUMERLING, A. A. DONALDSON, A. F. SMITH AND A. A. SHIVAS*

THE main problem affecting the treatment of breast cancer is that systemic spread to bones, liver, lungs, brain and other sites has taken place in the majority of patients who present with early disease. As with other malignancies, accurate determination of the extent of breast cancer will become an essential prerequisite to rational management, which must include consideration of systemic as well as local treatment.

The methods which are routinely applied to determine this are of low sensitivity. Routine radiographs of chest and skeleton and routine liver function tests detect unsuspected metastases only in a few patients with early disease. Emphasis has therefore been placed on the importance of determining the histological state of the axillary lymph nodes as an indicator of likely metastatic spread elsewhere. Those with proved node involvement are well known to have disease of bad prognosis, and therefore are eligible to be included in trials of systemic therapy (Fisher et al., 1969).

The development of more sensitive methods to detect otherwise occult metastatic disease in bones, liver and brain by isotope scintigraphy, ultrasonography and CT scans, by more sensitive liver function tests and by estimation of breakdown excretion products, e.g. urinary hydroxyproline, has stimulated interest in their use as staging methods in breast cancer.

In 1974, rather than use these techniques in an *ad hoc* way, we decided to carry out a prospective study in which all patients with early breast cancer attending our clinic had a strict programme of assessment before investigation. The objectives were to determine the proportion of patients with early disease in whom occult metastases would be suspected by these methods, to relate the findings to the histology of the lower axillary (pectoral) lymph nodes which were sampled at the time of primary treatment and to correlate both of these to the subsequent progress of the disease. The determination of 'operability' therefore did not include knowledge of the results of these tests but was by normal clinical staging.

Table I: TREATMENT PROTOCOL

Day 1	Start gelatin-free diet Radiological survey of skeleton Skeletal scintiscan Blood for alkaline phosphatase and γ-glutamyl transpeptidase
Day 2	Continue diet
Day 3	Continue diet First collection 24-h urine
Day 4	Continue diet Second collection 24-h urine Liver scintiscan Blood for alkaline phosphatase and γ-glutamyl transpeptidase

Patients and methods

Over 200 women with UICC stages I, II and operable III (T3 on size) breast cancer have been studied, all with negative chest and skeletal radiographs. This report is of the first 172 patients, all of whom have been regularly followed up for 1–4 years.

The investigations were carried out over a 4-day period in an assessment unit in a small 5-day hospital. These were designed to detect occult metastatic disease in bone and in liver and included skeletal scintigraphy, urinary hydroxyproline excretion on a gelatin-free diet, hepatic scintigraphy and estimations of plasma, γ-glutamyl transpeptidase and alkaline phosphatase. Except where indicated, the protocol remained constant for the whole study, the investigations being carried out on identical days (*Table I*).

Scintigraphy: All scans were performed using a Nuclear Enterprise mark IV gamma camera. The isotope used initially for skeletal imaging was ^{99}Tc^{m}-hydroxyethylidine disodium phosphate but latterly this has been ^{99}Tc^{m}-disodium etidronate stannous chloride (Osteoscan). Between 10 and 15 mCi were injected intravenously and 10–15 images taken at 3 h. These included anterior and posterior pelvis, right and left anteroposterior sternum, right lateral skull, lumbar, thoracic and cervical spine, right and left shoulder and ribs.

For liver imaging 2 mCi ^{99}Tc^{m}-sulphur colloid were injected intravenously and three images (anterior, lateral and posterior) taken after 15 min. All scans were first reported by members of the Department of Radiology but were subsequently reviewed along with skeletal X-rays by M. D. S. with E. L. M. C. or M. M. R. A positive bone scan was one in which there were areas of increased uptake which could not be explained by radiological evidence of benign disease. A positive liver scan was one showing areas of decreased uptake.

Urinary hydroxyproline: Patients were placed on a gelatin-free diet for 4 days and urine collected during days 3 and 4 into clean Winchester bottles containing 8 g boric acid as preservative. Estimates of hydroxyproline were performed by the methods of Ellis and Goldberg (1970). Creatinine was estimated by autoanalyser. The results were expressed as the total output of hydroxyproline in mg/24 h and as the hydroxyproline : creatinine ratio (mg/g creatinine). As a result of studies in normal women, abnormal values were set at $\geqslant 33{\cdot}0$ mg/24 h for total output and $\geqslant 31{\cdot}0$ mg for the hydroxyproline : creatinine ratio. For the purpose of this study, an abnormality of either one was regarded as an abnormal hydroxyproline excretion.

Once studies in 93 patients had established that there was no difference in the values of the collections taken on days 3 and 4 of the gelatin-free dietary period, only day 3 was used for collection and estimation.

γ-Glutamyl transpeptidase: This was estimated by a kinetic reaction at 37 °C using γ-glutamyl nitrolalide as substrate. A value of 35·0 units or more was taken as abnormal.

Alkaline phosphatase: This was estimated by autoanalyser using *p*-nitrophenyl acid phosphate as substrate. When abnormal values were depicted (>100 units per litre) polyacrylamide gel electrophoresis was used to determine whether these were due to bone or liver isoenzymes (Warwick et al.,

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Table II: INCIDENCE OF POSITIVE TESTS IN 172 PATIENTS WITH BREAST CANCER OF STAGES I, II AND OPERABLE III

	No. of patients
Suspected bone metastases	40
Scintiscan positive	12
Increased output urinary hydroxyproline or hydroxyproline : creatinine ratio	26
Elevated alkaline phosphatase	9
Suspected liver metastases	21
Scintiscan positive	11
Elevated γ-glutamyl transpeptidase	13
Elevated alkaline phosphatase	2

Table III: THE INCIDENCE OF SUSPECTED OCCULT METASTATIC DISEASE IN RELATION TO NODE STATUS

	No. of patients	No. with suspected metastases
Nodes involved by tumour	75	28 (37%)
Nodes not involved by tumour	73	20 (27%)
Nodes not identified by surgeon and/or pathologist	24	5 (21%)
Total	172	53 (31%)

χ^2 of nodes involved versus others, 2·774 $P<0{\cdot}10$.

Table IV: POTENTIAL VALUE OF TESTS FOR OCCULT DISEASE OVER NODE STATUS IN WHOLE SERIES OF 172 PATIENTS IN DEFINING DISEASE OF BAD PROGNOSIS

Definition of 'bad prognosis'	No. of patients	% of 172 patients
Nodes involved histologically (with or without positive tests)	75	44
Negative (or non-identified nodes) but positive tests	25	14
Total	100	58

1972). Initially two blood samples were taken from each patient for γ-glutamyl transpeptidase and alkaline phosphatase estimations. As there were no differences, a single sample was subsequently taken.

CT brain scans: A sample of 40 consecutive patients within this series had CT brain scans performed, seeking evidence of occult metastatic cerebral disease, either by focal areas of abnormal density or by the demonstration of discrete opacities.

Sodium diatrizoate (500 ml) (Urografin, Schering) was injected intravenously for contrast enhancement. Each patient had a total of 8 scans performed, 4 with contrast enhancement and 4 without, using initially an EMI mark I scanner and latterly a CT 1010 scanner.

Treatment

It was intended that all patients be treated in an identical way. In the event, 168 patients were treated by total mastectomy and pectoral (lower axillary) node sampling. On account of age, 3 had a local excision with axillary node biopsy and 1 was treated by radiotherapy alone. Nodes were identified for histological examination in 148 patients, of whom 75 had positive and 73 negative nodes. In the remaining 24 patients nodes were not identified by either the surgeon or the pathologist. All patients have been followed up at intervals of 4 months. A review of the records of all 172 patients was undertaken in March 1979 and the current state of all patients confirmed. No patient has been lost to follow-up.

Results

CT brain scans: None of the 40 patients investigated by CT brain scans had any abnormality demonstrated. For this reason this investigation was discontinued.

Table V: INCIDENCE OF RECURRENT DISEASE IN THOSE WITH OR WITHOUT POSITIVE TESTS FOR OCCULT METASTATIC DISEASE AT THE TIME OF MASTECTOMY

Status at mastectomy	No. of patients	No. with recurrence
Suspected metastatic disease bone or liver or both	53	14 (26%)
All tests negative	119	35 (29%)

χ^2 of difference 0 134.

Table VI: RELATIONSHIP BETWEEN RECURRENCE AT 1–4 YEARS, NODE STATUS AND TESTS FOR OCCULT METASTATIC DISEASE AT TIME OF MASTECTOMY

Node histology	Tests for occult disease	No. of patients	No. with recurrence
Positive	Positive	28	8 (35%)
Positive	Negative	47	23 (49%)
Negative or not identified	Positive	25	6 (24%)
Negative or not identified	Negative	72	12 (17%)

Suspected metastases in bone and liver: Forty of the 172 patients (23 per cent) had one or other test for bone involvement positive and therefore were regarded as having a suspicion of metastatic bone disease, 21 patients (12 per cent) had a suspicion of liver metastases on similar grounds and 53 patients (31 per cent) one or other or both. The incidence of abnormal tests is given in *Table II*. Only 1 of the 40 patients with suspected bone metastases had all three and 5 had two tests positive; only 1 of the 21 patients with suspected liver metastases had all three and 3 patients had two tests positive. The other 34 patients with suspected bone metastases and 17 with suspected liver metastases had only one abnormal test.

Relationship to node status: The relationship between positive tests and pectoral node histology is shown in *Table III*. Although there is a trend towards more positive tests in those with involved nodes than those with either negative or non-identified nodes, this does not reach statistical significance. These tests for occult metastatic disease, compared with information on node status only, defined an additional 14 per cent of patients who could be presumed to have disease of bad prognosis (*Table IV*).

Recurrence: Forty-nine of the 172 patients (28 per cent) have developed recurrent disease. The incidence is no greater in those suspected to have occult metastatic disease at the time of mastectomy than in those in whom tests for metastatic disease were negative (*Table V*). There is also a disappointing relationship between positive tests and the site of recurrence. Only 8 of the 40 patients with suspected bone involvement have developed overt bone metastases; and only 4 of 21 with suspected liver involvement have developed overt liver metastases. This incidence is less than that observed in the 119 patients in whom all tests proved to be negative, 35 of whom have developed overt bone or liver disease.

In *Table VI* the relationship between the incidence of positive tests for occult metastatic disease, node status (grouping negative and non-identified nodes together) and recurrence is given. Those with positive nodes have high recurrence rates irrespective of the results of the superstaging tests which have contributed little to the recognition of bad prognosis. In those patients with negative (or non-identified) nodes these tests for occult metastatic disease did appear to contribute to the definition of a good prognosis group and patients with negative (or non-identified) nodes and negative superstaging tests had a particularly low recurrence rate. However, this is not of statistical significance (Cant et al., 1977).

Conclusions

Although a longer follow-up is required to be certain of the validity of the conclusions, these data do suggest that a strict protocol of assessment of patients with early breast cancer for occult metastatic disease does not contribute to the definition of those with disease of bad prognosis. Although such tests were positive in 30 per cent of patients, they were of little additional value over the histological state of the axillary nodes, and at best would only identify a further 14 per cent of patients with potentially bad disease. Even this is doubtful, as the relationship between positive tests and subsequent recurrence is poor.

Meantime, the histological state of the axillary lymph nodes is still the best indicator of likely metastatic spread, and removal of nodes for histological examination is an essential part of the initial management of the disease, irrespective of the type of primary treatment.

References

CANT E. L., SMITH A. F., SUMERLING M. D. et al. (1977) Superstaging in breast cancer—a correlation of lymph nodes, histology and investigations designed to detect occult metastatic disease. *World J. Surg.* 1, 303–305.

ELLIS D. and GOLDBERG D. M. (1970) *Methods in Clinical Chemistry*. Basle, Karger, pp. 10–20.

FISHER B., SLACK N. H., BROS I. D. J. et al. (1969) Cancer of the breast: size of neoplasm and prognosis. *Cancer* 24, 1071–1081.

WARWICK R. R. G., SHEARMAN D. G. C., PERCY ROBB I. W. et al. (1972) Electrophoretic separation of alkaline phosphatase isoenzymes; a clinical evaluation. *Scott. Med. J.* 17, 172–175.

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Bone scanning: its lack of value in the follow-up of patients with breast cancer

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SUMMARY

Three hundred and fifty-four women with primary operable breast cancer had a bone scan performed within 6 weeks of a simple mastectomy. Eight (2·3 per cent) were positive, but 7 of these patients had radiological evidence of bony metastases. Follow-up bone scans 1 year postoperatively on 278 patients showed only 12 (4·3 per cent) positive, and of these, 9 had other radiological evidence of metastatic disease. At 2 years postoperatively there were 13 (9·2 per cent) positive bone scans amongst 141 patients. Only 2 of these 13 had no other evidence of metastases. Although a bone scan is a useful investigation in patients with bone pain, there is no place for routine bone scanning in either the staging or follow-up of women with operable breast cancer.

THE incidence of positive bone scans performed at the time of mastectomy in patients with clinically operable breast cancer is reported in different series as varying from 1·9 to 20·2 per cent (British Breast Group, 1978). In spite of this unexplained disparity, a bone scan is still the most sensitive method of showing symptomatic bony metastases (Sklaroff and Charkes, 1968; Citrin et al., 1975; Galasko, 1975). In 1975 Galasko reported that 24 per cent of 50 patients with apparently 'early' breast cancer had a positive bone scan at the time of mastectomy. He went on to show that 83 per cent of those patients with a positive scan were dead within 5 years of mastectomy, an observation confirmed by Campbell et al. (1976) and McKillop et al. (1978). McKillop and co-workers concluded that serial bone scanning is of considerable value in the follow-up of these women and that a positive bone scan is a bad prognostic sign.

It has previously been reported from Nottingham (Davies et al., 1977) that although a positive scan is a bad prognostic finding, it identifies only a few of those patients who subsequently develop a major recurrence and that lymph node biopsy at the time of mastectomy gives a great deal more information in this respect.

In this paper further experience with bone scans performed in Nottingham is reported together with the results of sequential bone scans in the first 2 years following mastectomy.

Patients and methods

Between 1973 and 1978, 354 patients aged between 26 and 75 years with primary operable breast cancer were admitted under the care of one surgeon (R. W. B.). Patients were considered to have primary operable breast cancer if they had a breast tumour that was less than 5 cm in diameter on clinical examination, with no clinical evidence of distant metastases. All the patients underwent a simple mastectomy with biopsy of the axillary, apical and internal mammary nodes. A base line bone scan, chest X-ray and skeletal survey were performed within 6 weeks of operation. Postoperatively the patients were followed up in a special post-mastectomy clinic at 3-monthy intervals for 18 months and thereafter at 6-monthly intervals. At each attendance the patients were examined clinically and blood was taken for haemoglobin, white cell count, ESR, liver function tests and calcium levels. An annual bone scan and chest X-ray were performed on each patient. Any areas of increased or abnormal uptake demonstrated by the scan were then examined by conventional radiographs. Patients were scanned with either an Ohio Nuclear Rectilinear scanner or a Searle LFOV gamma camera; ^{99}Tc^{m} polyphosphates and diphosphonates have been used throughout the study. The first 87 patients were scanned by the X-ray Department at the General Hospital, Nottingham. The three subsequent cohorts consisted of 94, 78 and 95 patients each and were all scanned by the X-ray Department at the City Hospital, Nottingham. Only the fourth cohort, 95 patients, has been scanned with the gamma camera. Three possible interpretations of the scans were allowed: negative for bony metastases, equivocal and positive for bony metastases. In this paper an equivocal result has been classed as negative (Davies et al., 1977).

Results

At the time of mastectomy

Three hundred and fifty-four patients had a bone scan performed in the immediate postoperative period. Of these, only 8 (2·3 per cent) were positive (*Table I*). Seven out of these 8 patients had metastases visible on conventional X-rays done at the same time as the scan. Only 1 patient out of 354 (0·3 per cent) had a positive bone scan without radiological evidence of metastases. This patient had no other evidence of distant metastases at the time of her mastectomy (she did have lymph node invasion at mastectomy). Three months later, she developed an oculomotor palsy and this was shown by a brain scan to be due to a cerebral metastasis.

One patient had radiological evidence of sclerotic bony metastases at the time of mastectomy which the bone scan failed to demonstrate—in other words, a false negative result. A year later these metastases were picked up by the bone scan. The patient's X-rays at that time showed considerable progression of the lesions.

Four patients (1·1 per cent) had a false positive bone scan result, i.e. their scans were classified as being positive for bony metastases. However, after a minimum follow-up of 30 months, sequential scans and X-rays have shown these 'hot spots' either to disappear completely or else to remain unchanged; clinically all 4 patients remain well with no clinical evidence of recurrence. It seems reasonable to assume that these are genuine false positive results.

At 1 year postoperatively

To date 278 patients have had a bone scan performed 1 year postoperatively, with a positive result in 12 (4·3 per cent) (*Table II*). Of those 12 patients, 7 had bony metastases visible on plain X-rays. Two patients had a positive bone scan, and although bony metastases could not be detected by conventional radiographs, their chest X-rays showed lung metastases. Only 3 out of 278 patients (1·1 per cent) had a positive bone scan with no other radiological evidence of metastases. Of these 3 patients, 1 developed clinically apparent liver metastases 6 months later, 1 started to develop bone pain a year after her scan became positive and only at this time did her X-rays confirm the presence of osteolytic metastases and the third remains well 3 months after her positive bone scan result with no evidence of metastases on X-ray.

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At 2 years postoperatively

Not enough patients in the fourth cohort have yet been scanned at 2 years to be included in an analysis of our results, therefore the results for scans done at 2 years are taken from the first three cohorts only (*Table III*). To date, 141 patients have had a bone scan performed at 2 years. Thirteen scans (9·2 per cent) were positive. Six of these 13 patients had bony metastases visible on conventional X-rays done at the same time. One of these 13 had obvious lung metastases on her chest X-ray. Three patients in this group had developed clinical evidence of soft tissue metastases before the demonstration of occult bony metastases on the routine scan. Therefore only 2 patients (1·4 per cent) had a positive bone scan with no other evidence of metastases. In 1 patient the interval between the positive bone scan and clinical evidence of metastases was 19 months, the other remains well with no X-ray or clinical evidence of recurrence 1 year after her positive bone scan.

Discussion

Scanning at the time of mastectomy

In Nottingham the incidence of positive bone scans at the time of mastectomy is 2·3 per cent—the previous report on only 192 cases put the figure at 4·7 per cent (Davies et al., 1977). These results are in the same range as the results reported by Green et al. (1973), Lentle et al. (1975), El-Domieri and Shroff (1976), Baker et al. (1977) and Gerber et al. (1977). This low percentage of positive results is in sharp contrast to the very much higher figures obtained by Campbell et al. (1976), Roberts et al. (1976) and McKillop et al. (1978).

The statement on bone scanning published by the British Breast Group (1978) revealed a very wide variation in the reported incidence of positive bone scans. Two London centres, Guy's and Charing Cross, had between them the lowest and highest rates respectively: 1·9 per cent for Guy's and 20·2 per cent for Charing Cross. The very wide difference in the percentage of positive bone scans found at the time of mastectomy by different authors is an important and unsolved problem.

Although 2·3 per cent of our initial scans were positive, only 1 (0·3 per cent) was positive without other X-ray evidence of metastases at the same site. This represents an enormous effort for a very tiny yield of information. Another point to emerge from scanning at the time of mastectomy is that there are nearly as many false positive as true positive scans. Approximately 40 per cent of patients with operable breast cancer will be dead or will have had a major recurrence within 5 years of operation (Brinkley and Haybittle, 1975). It is difficult to see how, with a positive incidence of 2·3 per cent, bone scanning can seriously be considered as contributing to the initial overall prognosis of patients with breast cancer. All a positive bone scan suggests is that that particular patient will do very badly in terms of morbidity and mortality.

Table I: EARLY POSTOPERATIVE BONE SCAN RESULTS ($n = 354$)

	Cohort 1st	2nd	3rd	4th	Total
Positive	2	2	1	3	8 (2·3%)
Negative	83	90	76	92	341 (96·3%)
False positive	2	2	0	0	5 (1·1%)
False negative	0	0	1	0	1 (0·3%)

Table II: BONE SCAN RESULTS IN THE FIRST POSTOPERATIVE YEAR ($n = 278$)

	Cohort 1st	2nd	3rd	4th	Total
Positive	2	4	4	2	12 (4·3%)
Negative	72	81	66	43	262 (94·2%)
False positive	1	0	0	0	1 (0·4%)
False negative	1	1	0	1	3 (1·1%)

Table III: BONE SCAN RESULTS 2 YEARS POSTOPERATIVELY ($n = 141$)

	Cohort 1st	2nd	3rd	Total
Positive	6	6	1	13 (9·2%)
Negative	56	58	12	126 (89·4%)
False positive	1	0	0	1 (0·7%)
False negative	1	0	0	1 (0·7%)

To date not enough patients in the fourth cohort have been scanned at 2 years to be included (*see* text).

Table IV: BONE SCAN RESULTS

	Postop. ($n = 354$) (%)	1st year ($n = 278$) (%)	2nd year ($n = 141$) (%)
Positive	2·3	4·3	9·2
Negative	96·3	94·2	89·4
False positive	1·1	0·4	0·7
False negative	0·3	1·1	0·7

Scanning 1 year after mastectomy

The conclusion at the end of the first year must be that the incidence of positive bone scan results is still very low (4·3 per cent) and if those patients with positive X-rays are discounted, then the 'scan only' positive results number only 3 out of 278 (1·1 per cent).

Scanning 2 years after mastectomy

The incidence of positive bone scans at 2 years is 9·2 per cent. However, if those patients with other evidence of metastases at the time of scanning are excluded, then the percentage of 'scan only' positive results is 1·4 per cent. Once again, a very small yield of useful information for a great deal of effort.

General conclusion

Differences in patient selection and methodology are a possible explanation for the widely differing reported incidence of positive bone scans. In Campbell's series, the 'equivocal' group of results were classed as positive, but even without combining these two groups, Campbell found a positive incidence of 26·25 per cent—ten times our figure of 2·3 per cent.

In the Nottingham study (*Table IV*) only patients with primary operable breast cancer under the age of 75 years have been included. The incidence of positive bone scans will be much greater in those with more advanced disease, and possibly also in the elderly. Gerber's patients were all 'recipients of no-cost military medical care' (Gerber et al., 1977). This led those authors to conclude that the low incidence of positive scans in his group (1·8 per cent) was because the patients, by not having to pay directly, were presenting themselves much earlier. Our results are similar to Gerber's and our patients also do not pay for their treatment. Nevertheless, two other British series (Campbell et al., 1976; Roberts et al., 1976) both report a far higher incidence of positive scans.

Citrin et al. (1974) have pointed out the considerable advantages of a gamma camera over a rectilinear scanner. Our recently acquired gamma camera is much preferred to the rectlinear scanner; nevertheless, the results are comparable with both systems. Furthermore, it does not appear that the low number of positive scans is a technical fault. Positive bone scans have been obtained in patients with bone pain from metastatic breast cancer but in whom conventional X-rays were negative. Hence the radiologists can and do diagnose bony metastases on a scan, confirming the presence of metastatic disease in breast cancer.

A further worrying conclusion from this study is the demonstration of how little relevance a positive bone scan result has to the management of the asymptomatic patient. In 1978, Baker wrote '. . . to my knowledge, there is no evidence that the detection and treatment of small asymptomatic bone metastases will necessarily increase either the length, or the quality of survival of patients with breast cancer'.

Although bone scans do detect metastases, it should be stressed that the number of asymptomatic patients with these early lesions is extremely small. Furthermore, each scan costs on average £30 to perform, hence the 773 scans in our series have cost £23 190. Routine bone scanning in breast cancer is increasingly being used throughout the country, but this is difficult to justify when the yield of useful information from the routine use of this investigation is so derisory.

References

BAKER R. R. (1978) Pre-operative assessment of the patient with breast cancer. *Surg. Clin. North Am.* **58**, 681–691.

BAKER R. R., HOLMES E. R., ALDERSON P. O. et al. (1977) An evaluation of bone scans as screening procedures for occult metastases in primary breast cancer. *Ann. Surg.* **186**, 363–367.

BRINKLEY D. and HAYBITTLE J. L. (1975) The curability of breast cancer. *Lancet* **2**, 95–97.

BRITISH BREAST GROUP (1978) Bone scanning in breast cancer. *Br. Med. J.* **2**, 180–181.

CAMPBELL D. J., BANKS A. J. and OATES G. D. (1976) The value of preliminary bone scanning in staging and assessing the prognosis of breast cancer. *Br. J. Surg.* **63**, 811–816.

CITRIN D. L., BESSENT R. G., GREIG W. R. et al. (1975) The application of the ^{99}Tc^{m} phosphate bone scan to the study of breast cancer. *Br. J. Surg.* **62**, 201–204.

CITRIN D. L., BESSENT R. G. and TUOHY J. B. (1974) Bone scanning in malignant disease. *Br. J. Hosp. Med.* **11**, 424–433.

DAVIES C. J., GRIFFITHS P. A., PRESTON B. J. et al. (1977) Staging breast cancer: role of bone scanning. *Br. Med. J.* **2**, 603–605.

EL-DOMIERI A. A. and SHROFF S. (1976) Role of pre-operative bone scanning in carcinoma of the breast. *Surg. Gynecol. Obstet.* **142**, 722–724.

GALASKO C. S. B. (1975) The significance of occult skeletal metastases, detected by skeletal scintigraphy, in patients with otherwise apparently 'early' mammary carcinoma. *Br. J. Surg.* **62**, 694–696.

GERBER F. H., GOODREAN J. J., KIRCH P. T. et al. (1977) Efficacy of pre-operative and post-operative bone scanning in the management of breast cancer. *N. Engl. J. Surg.* **297**, 300–303.

GREEN D., JEREMY R. and TOWSON J. (1973) The role of fluorine-18 scanning in the detection of skeletal metastases. *Aust. NZ J. Surg.* **43**, 251–254.

LENTLE B. C., BURNES P. E., DIERICH H. et al. (1975) Bone scanning in the initial assessment of carcinoma of the breast. *Surg. Gynecol. Obstet.* **141**, 43–47.

MCKILLOP J. H., BLUMGART L. H., WOOD C. B. et al. (1978) The prognostic and therapeutic implications of the positive radionuclide bone scan in clinically early breast cancer. *Br. J. Surg.* **65**, 649–652.

ROBERTS J. G., GRAVELLE I. H., BAUM M. et al. (1976) Evaluation of radiography and isotopic scintigraphy for detecting skeletal metastases in breast cancer. *Lancet* **1**, 237–239.

SKLAROFF D. M. and CHARKES N. D. (1968) Bone metastases from breast cancer at the time of radical mastectomy. *Surg. Gynecol. Obstet.* **127**, 763–768.

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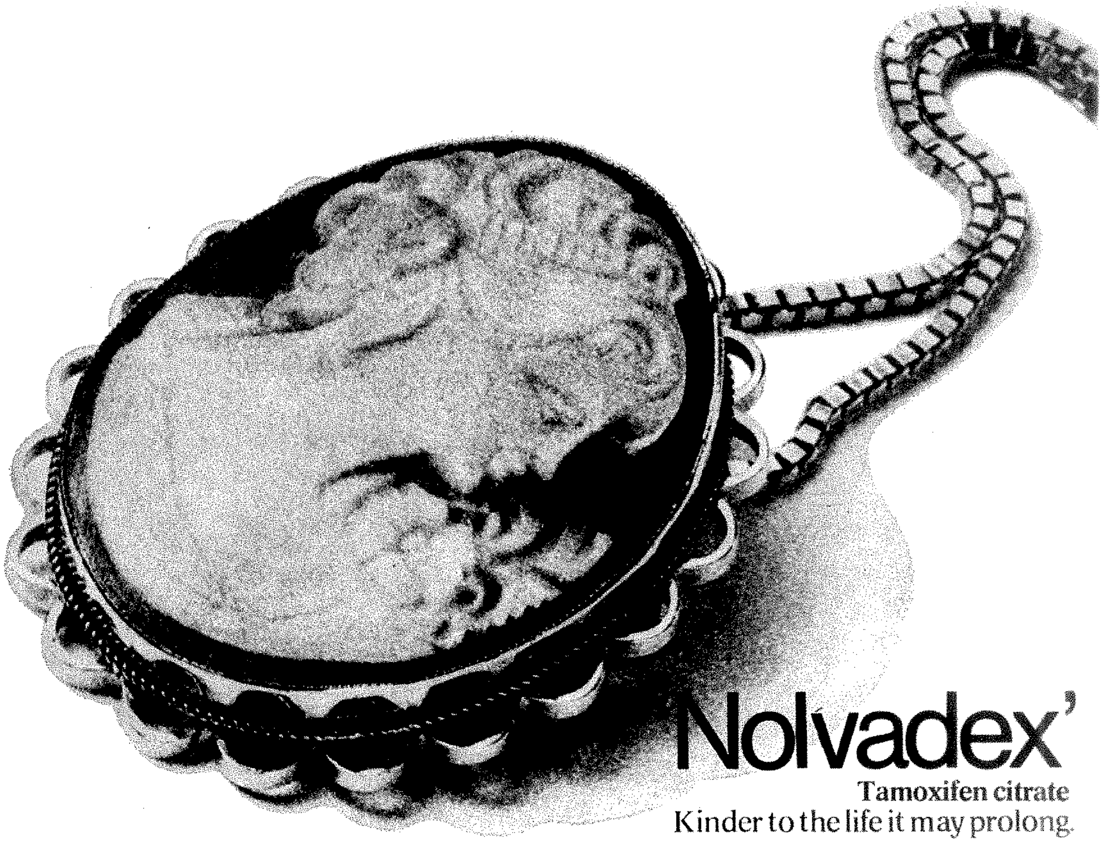

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[1] *Ann. intern. Med.* (1977), **87**, 404. [2] *Brit. med. J.* (1977), **2**, 1302. [3] *J. Urol.* (1977), **117**, 690.

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Joint Meetings of the Association of Surgeons of Great Britain and Ireland and the Royal Australasian College of Surgeons, 3–18 February 1979

DURING February 1979 a group of surgeons representing the Association of Surgeons of Great Britain and Ireland attended joint scientific meetings in Australia and New Zealand. This was a unique occasion as the Association had never before held a metting outside the United Kingdom and Eire.

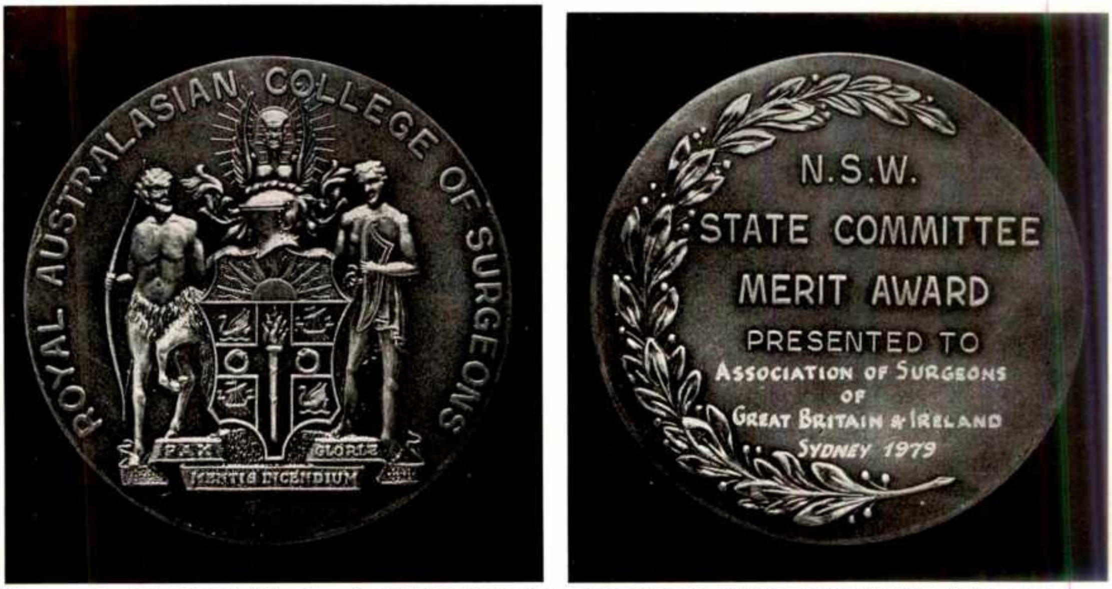
A party of 61, including 20 wives, left Heathrow Airport on the morning of Sunday 4 February, unfortunately 24 hours late due to reputed undercarriage trouble in the Jumbo jet. Following a further delay in Bombay, because of flight-deck computer problems, the party arrived in Perth early on Monday afternoon, after the scientific meeting had already commenced that morning. To enable members of our party to combat jet lag, an amended programme permitted the British papers to be presented the following day.

The joint meeting held on Tuesday and Wednesday 6 and 7 February was at the invitation of the Royal Australasian College of Surgeons in commemoration of the 150th anniversary year of the foundation of the state of Western Australia. The conference took place in the Sheraton Hotel in Perth, being organized by Professor Bernard Catchpole, who was well known to most of the party from his former days in Manchester and at St Bartholomew's Hospital, London. Surgical papers were presented by both Australian and British surgeons, covering various topics on general surgery.

Members of the Association and their wives were generously entertained during our short stay in Perth, and immediately after our arrival on the first evening we enjoyed a steak barbecue at the water's edge at the Royal Perth Yacht Club. Although many members were entertained privately by old friends, on the second evening the majority of our group undertook a delightful sail along the Swan River to Freemantle, the port of Perth, culminating in a seafood repast at the Oysterbed Restaurant.

On the final evening in Perth the conference dinner was held in the Sheraton Hotel, the main speaker being Professor G. Douglas Tracey, Junior Vice-President of the Royal Australasian College of Surgeons, who proposed the toast to the Association of Surgeons. The President of the Association, Mr Alan Birt, CBE, responded and expressed our great pleasure in being present on this auspicious occasion.

The following day the British party left on a 4-hour flight across the deserts of Australia to Sydney for a 2-day scientific meeting which was held in the Wentworth Hotel. This was a joint meeting of our Association in conjunction with the Annual Scientific Meeting of the New South Wales State Committee of the Royal Australasian College. The British party was welcomed on the first morning by Professor John Ham and our great friend, Sir John Lowenthal. The meeting was extremely well attended by the Australian surgeons and, as in Perth, the standard of papers read by both the Associations was consistently high. At the conclusion of the meeting Professor Ham presented the Association of Surgeons with the Medal of the New South Wales State Committee. This Medal is normally presented each year to the author of the best paper given at their scientific meeting, but to mark this historic occasion, it was awarded to the Association of Surgeons of Great Britain and Ireland



Photographs of the Medal of the New South Wales State Committee of the Royal Australasian College of Surgeons.

as a group. The Medal was accepted on behalf of the Association by Mr Adrian Marston, in the absence of Mr Alan Birt who was unfortunately confined to his bed with a virus infection.

The hospitality extended by the Australians in Sydney was exceptional, everyone in the British party being entertained either in a private house or club in in the city of Sydney.

On Sunday 11 February the majority of the British group, together with many of our hosts, spent the whole day on a cruise of the harbour and the numerous attractive bays around which Sydney is situated. Several members were fortunate enough to be able to attend the Sixth Test Match between England and Australia, played at the Sydney Oval. In glorious sunshine the party took great delight in watching the England side bat, but play was drawn to a close rather suddenly at the tea interval because of a hurricane-like storm.

During the final day in Sydney many members visited hospitals in the Sydney area. Mr G. J. Hadfield and the author made a short visit by air to the Royal Australasian College of Surgeons in Melbourne. They were received and conducted around the College by Council Member Professor Richard C. Bennett of Melbourne and by Mr R. Chapman, Secretary of the Australasian College. On the last evening in Sydney the British party, together with our Australian hosts, visited the famous Opera House, dining in the restaurant which overlooks the harbour and Sydney's renowned bridge. We then witnessed a spectacular performance by the Australia Opera Company of Franz Lehar's opera 'The Merry Widow', with Miss Joan Sutherland in the title role. This was a memorable occasion on our final evening in Australia.

On Tuesday 13 February we boarded our Jumbo jet for New Zealand and arrived in Auckland in the early evening. The following day a joint scientific meeting was held at the Royal Hospital, organized by Professor E. M. Nansen, and papers were read by both British and New Zealand surgeons. The remaining two days in New Zealand were taken up mainly by sightseeing and included an unforgettable visit to the Maori village in Rotorua, where we were fascinated by the volcanic hot springs.

On Saturday 17 February, a tired but happy party left on a long non-stop flight to Singapore, spending 24 hours in this far-Eastern centre. During the first evening many of us visited the famous Raffles Hotel, sampling a Singapore gin sling, before partaking of a traditional Chinese meal on the side-walk of Albert Street. On the final day members of the Association enjoyed a tour of the city, plus another Chinese meal, and in the afternoon a cruise around the harbour of Singapore before finally departing for London via Bahrain in the late evening.

This was a memorable stimulating tour, with excellent scientific meetings, magnificent scenery, renewal of old friendships and hospitality without precedent.

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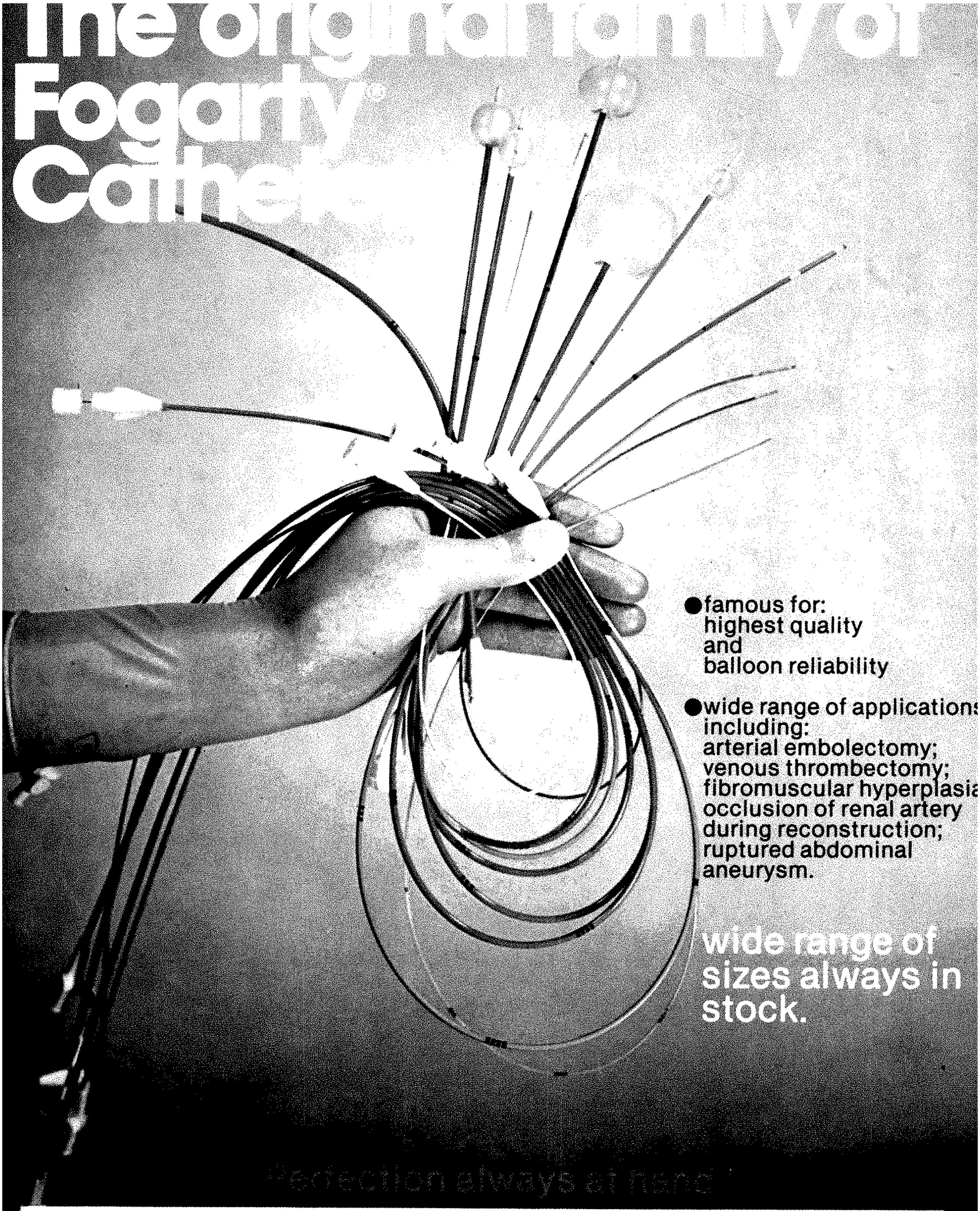

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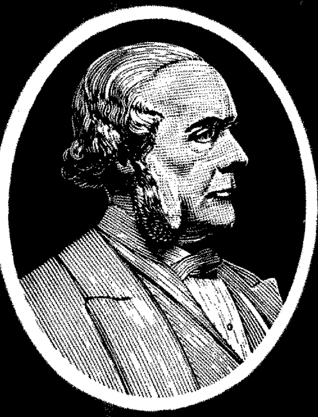

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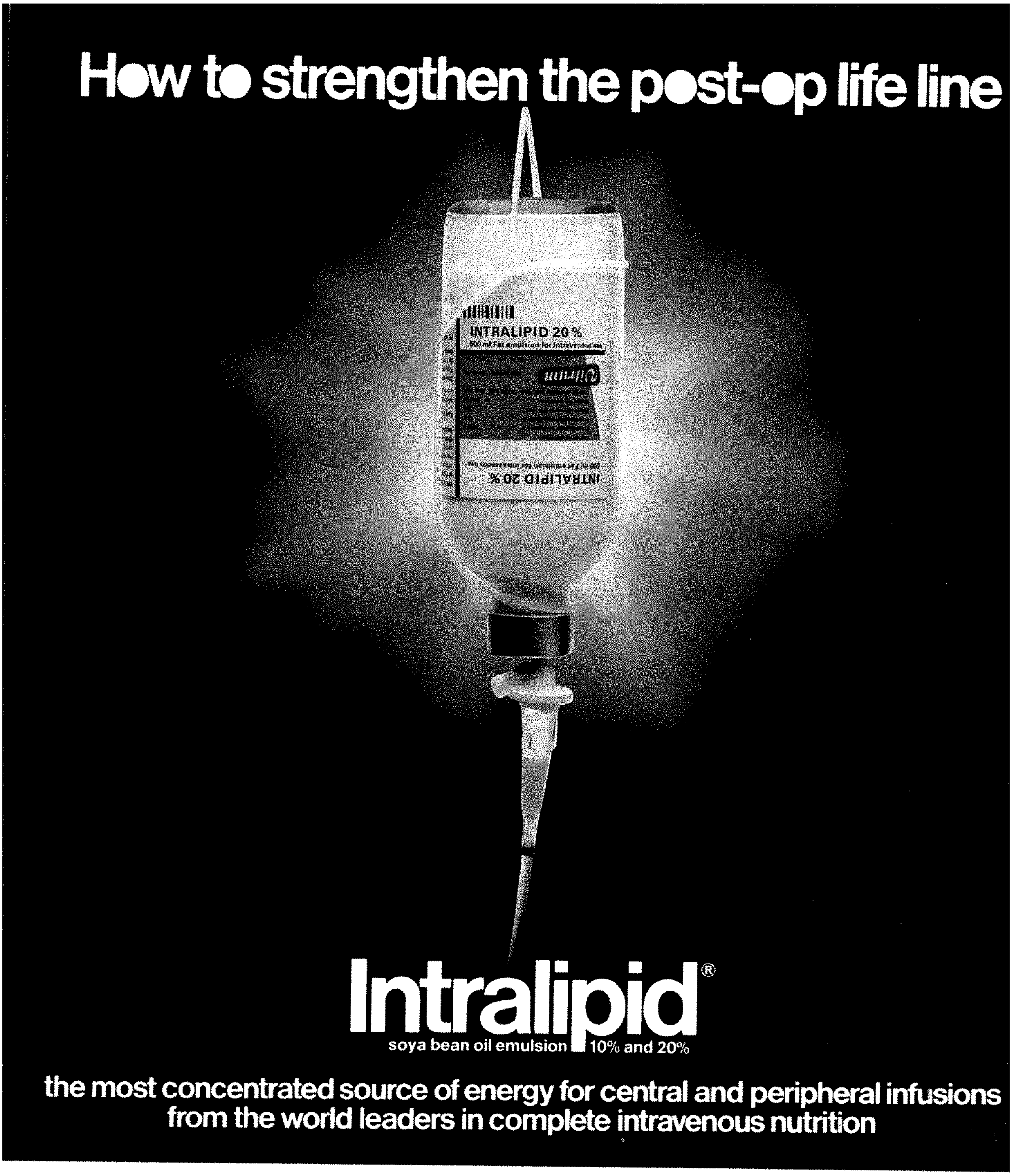
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Dosage and administration Intralipid 10%: 500–1,500 ml daily in conjunction with intravenous amino-acids. For increased caloric requirements Intralipid 20%: 500–1,500 ml daily in conjunction with amino-acids. Intralipid 10% and 20% are administered by slow intravenous infusion. During the first 10 minutes the drip rate should be adjusted to 20 drops per minute and after half an hour this can be adjusted to a final rate of 60 drops per minute. 500 ml of either emulsion should be given in not less than three to five hours on the first day of infusion. On the first day of infusion it is advisable to administer 10 ml Intralipid 10% or 5 ml Intralipid 20% per kg body weight. Subsequently the dose is usually doubled, and when a larger intake is indicated it may be increased to 3 g fat per kg body weight.

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Contra-indications, warnings, etc. Intralipid is contra-indicated in pathological hyperlipaemia and severe liver damage.

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Pharmaceutical precautions Store at a temperature between 4°C and 8°C, and do not use after the date of expiry indicated. The contents of each bottle are for a single infusion and any residual emulsion should be discarded. No drugs should be added to Intralipid prior to or during infusion.

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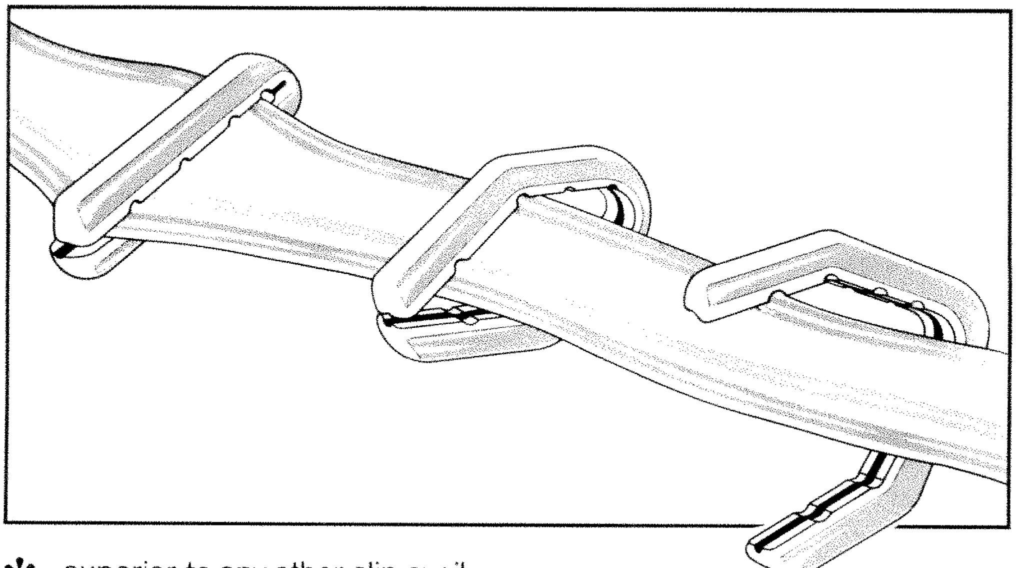

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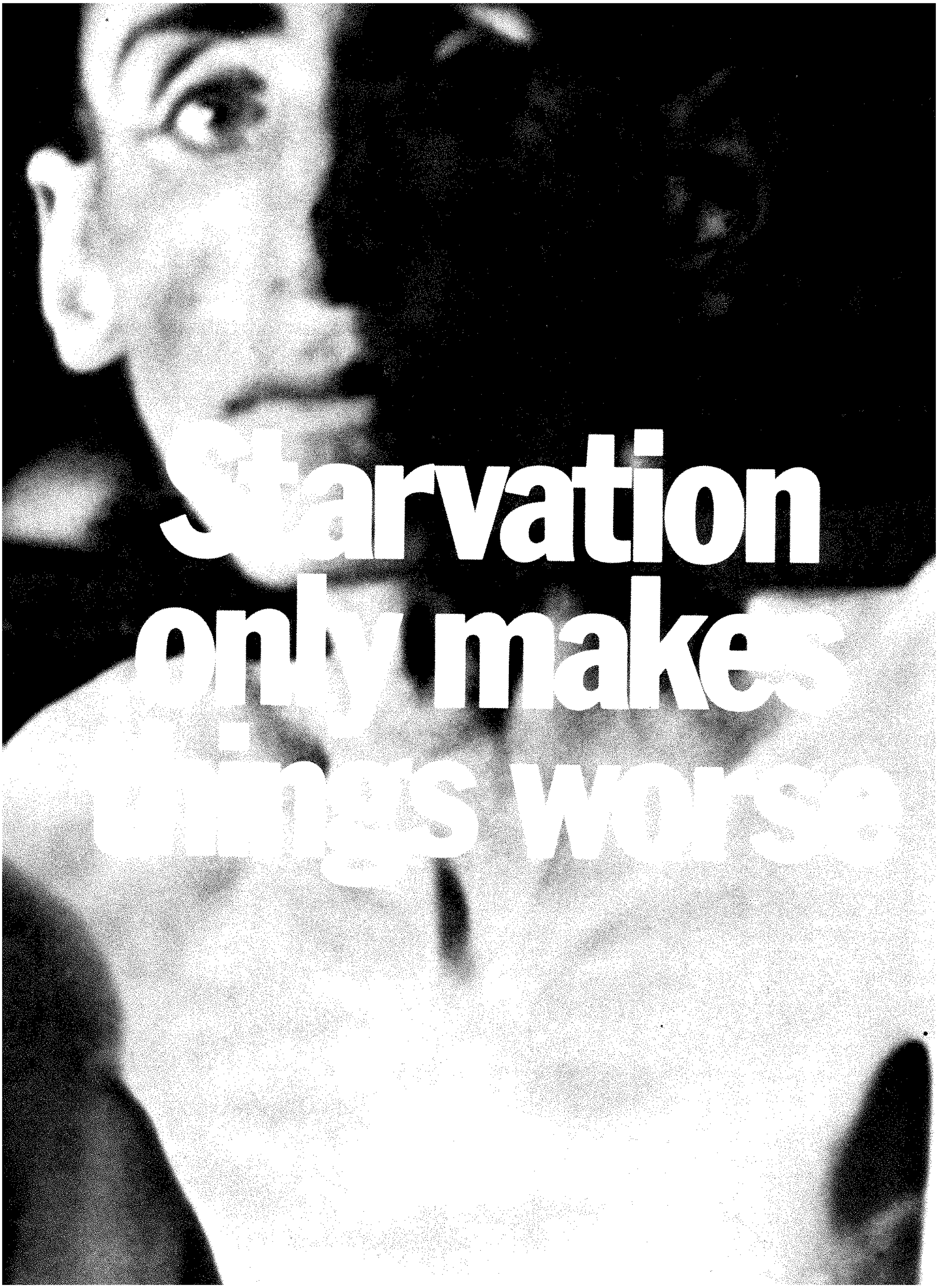
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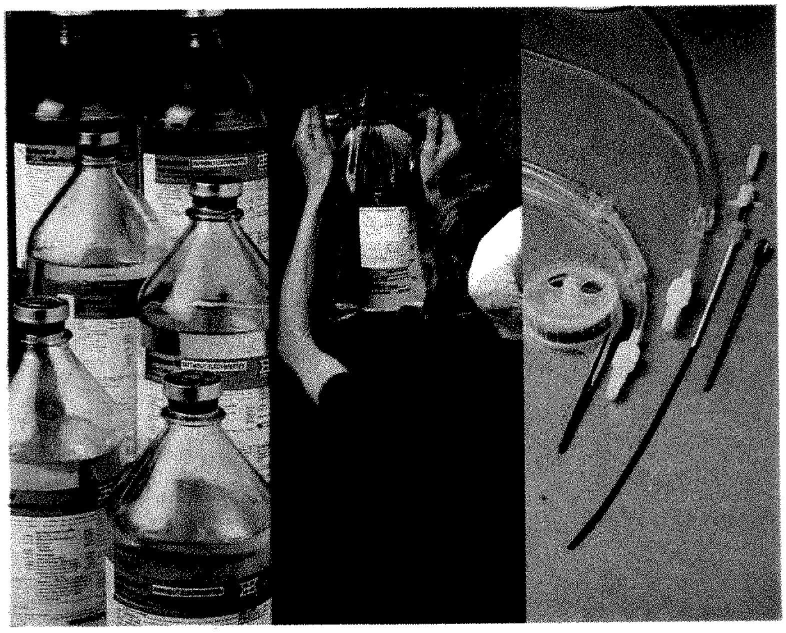

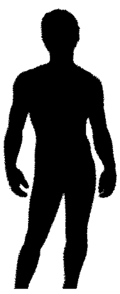

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References
1. Daly, J.M., Vars, H.M., and Dudrick, S.J. (1972). Effects of protein depletion on strength of colonic anastomoses. Surgery Gynec. Obstet., *134*, 15-21.
2. Alexander, J.W. (1974). Emerging concepts in the control of surgical infections. Surgery, *75*, 934-946.
3. Silk, D.B.A. (1978). Clinical nutrition in hospital – 1. Principles Hospital Update, *4*, 483-489.

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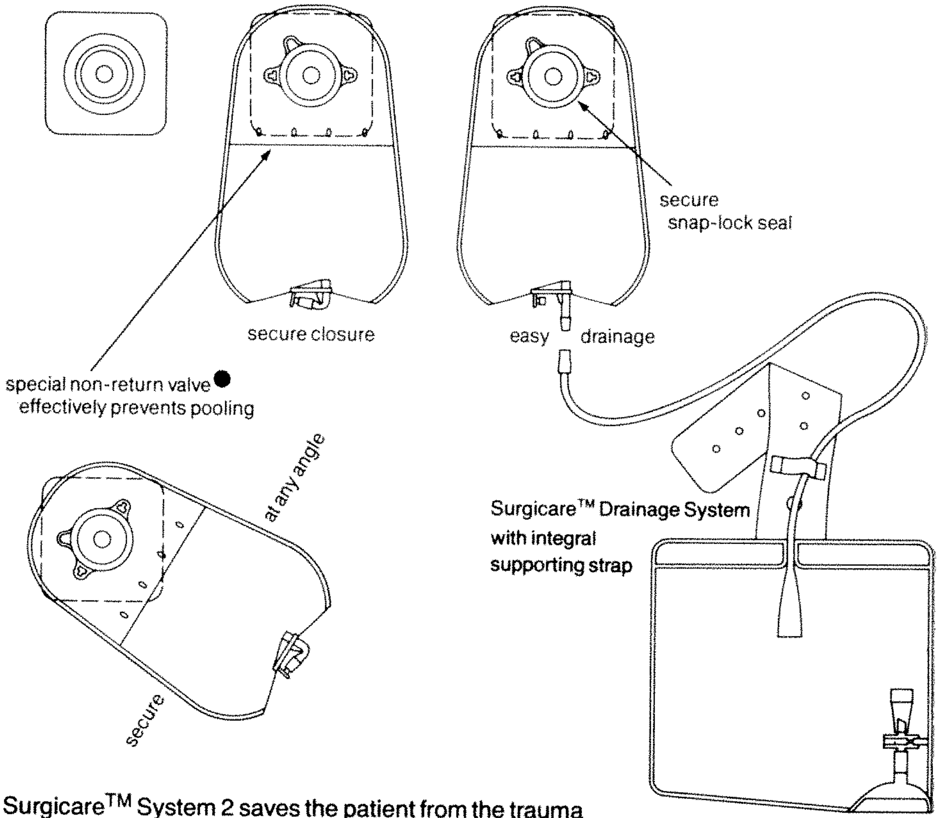

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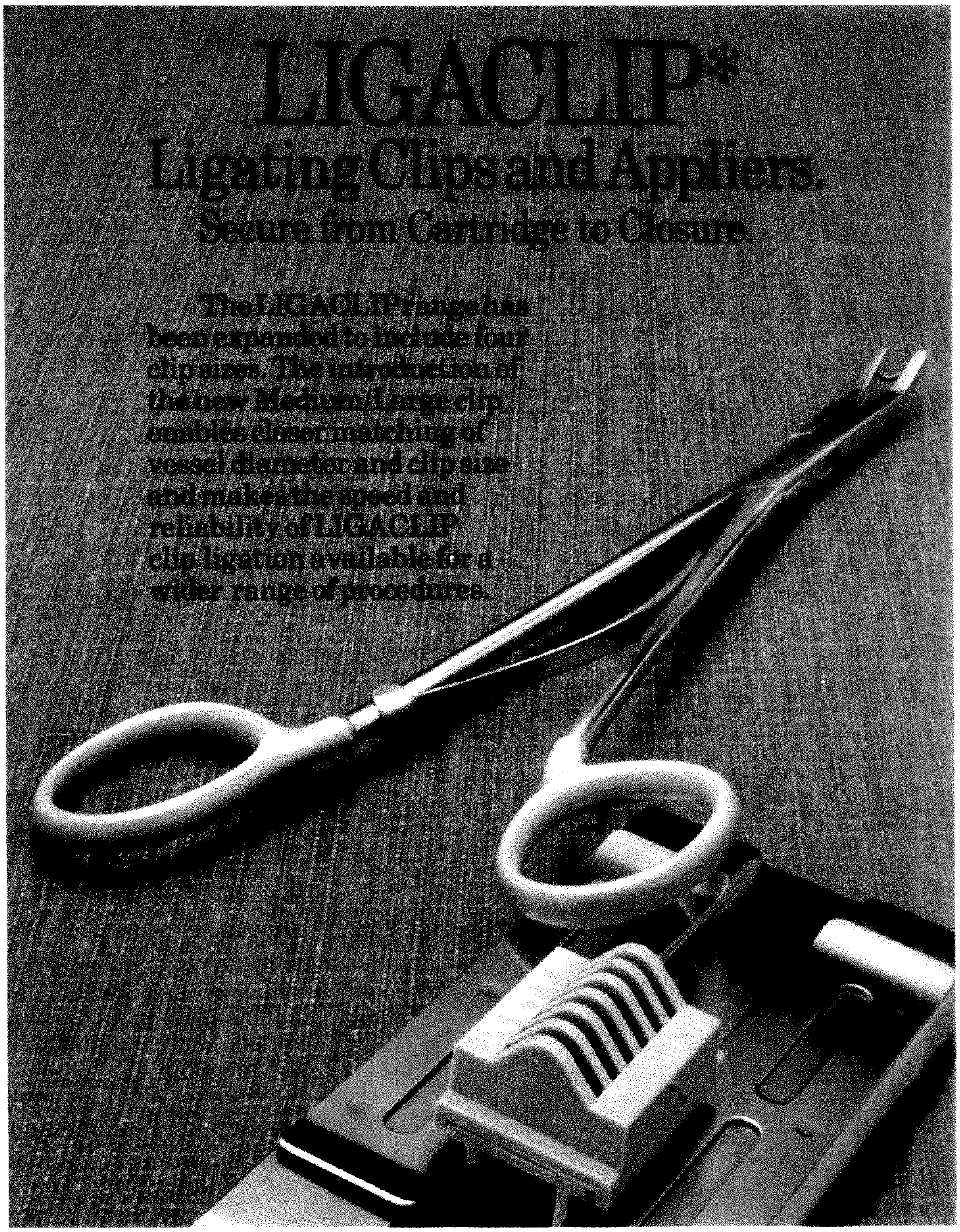

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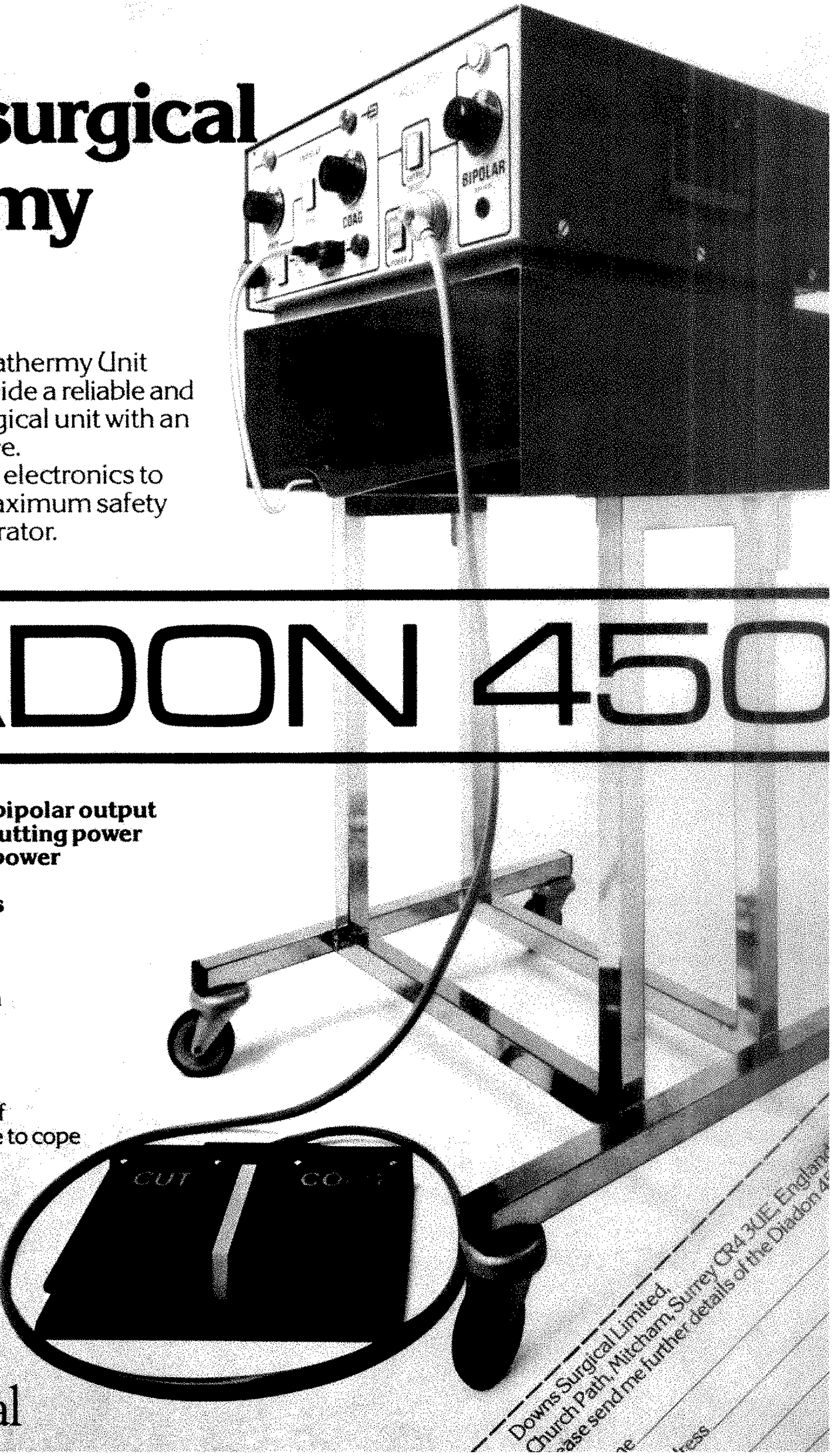

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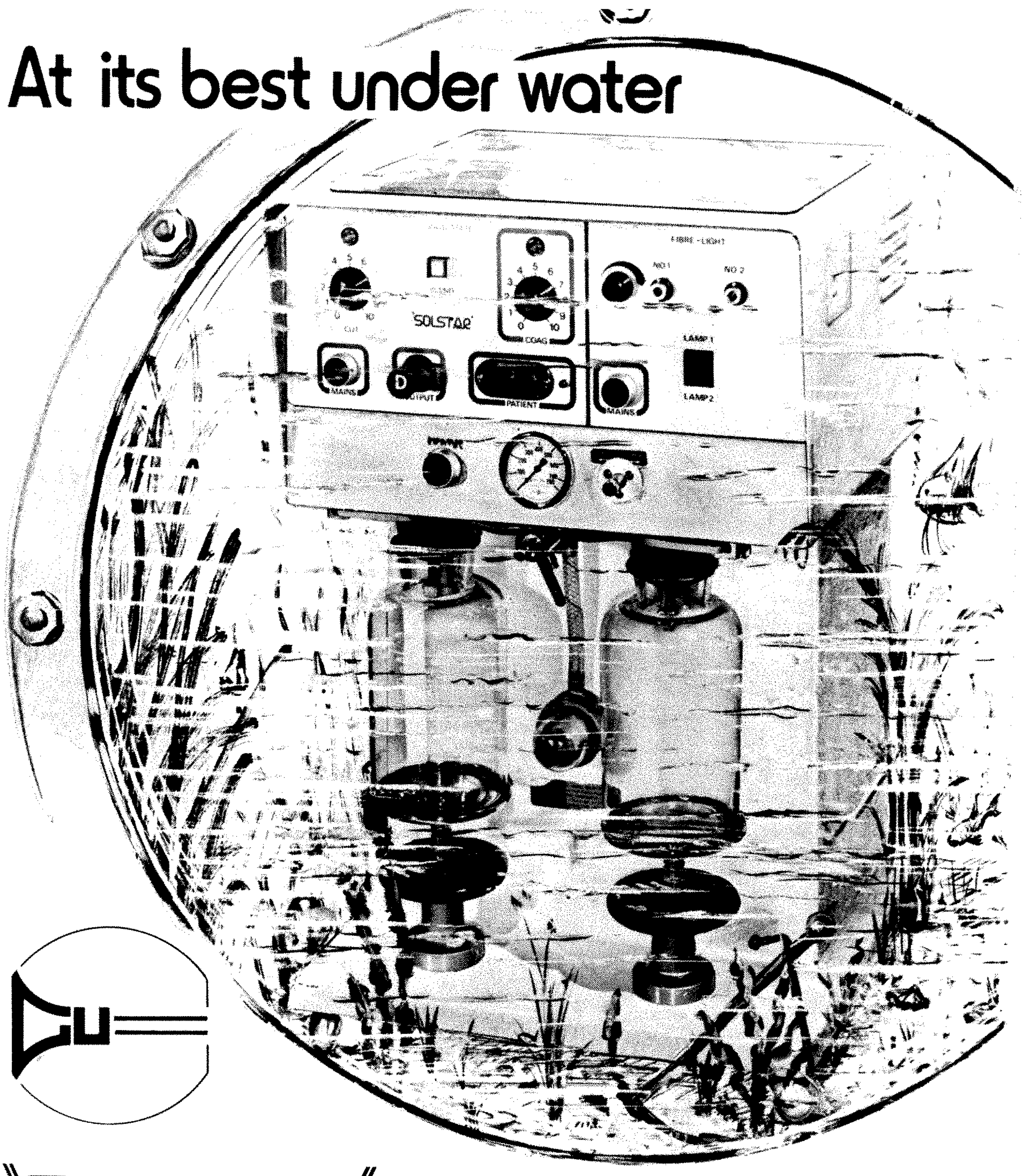

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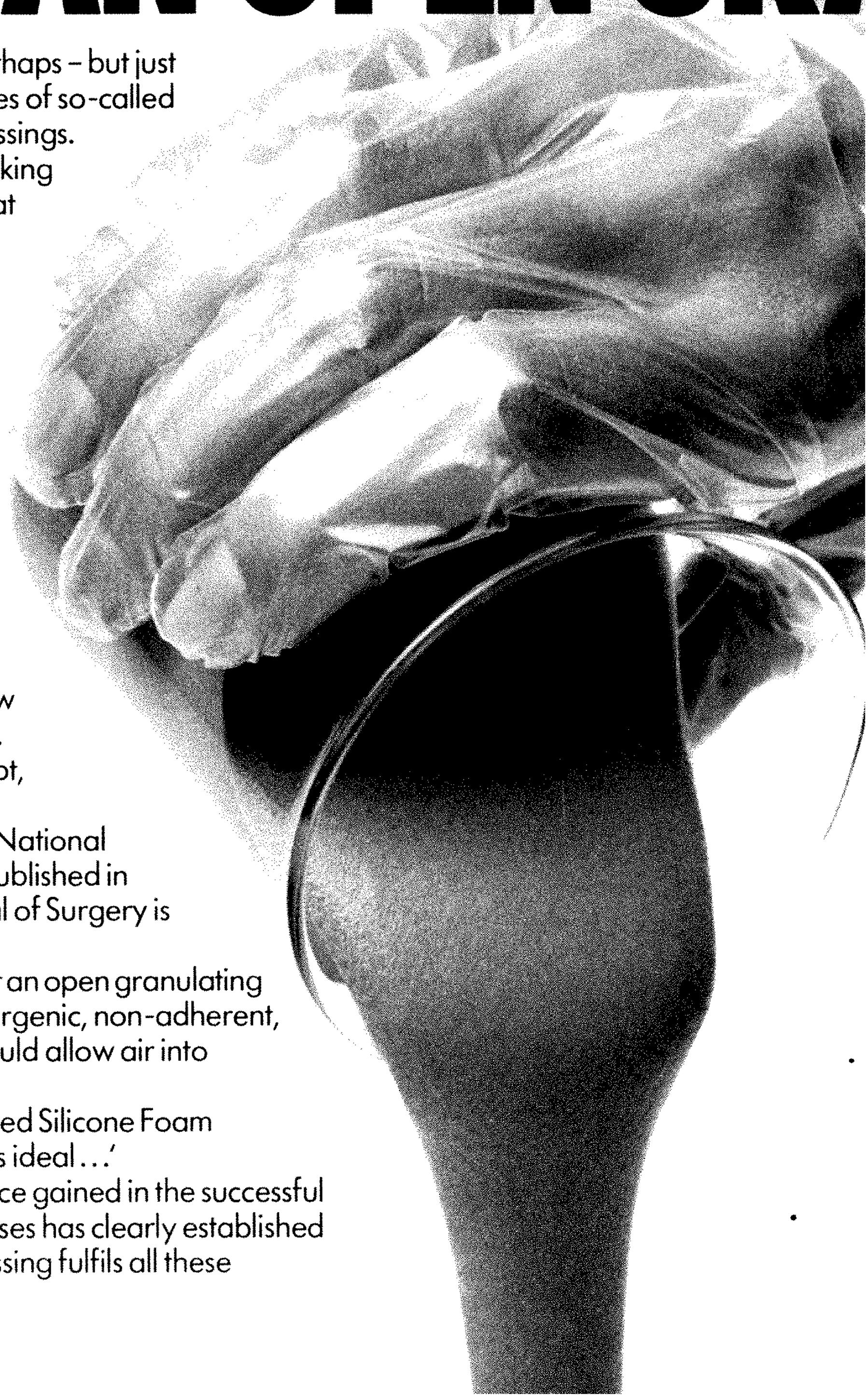

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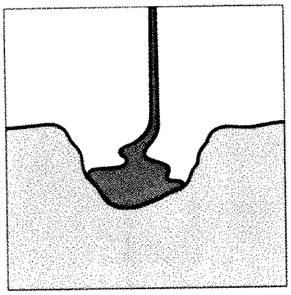

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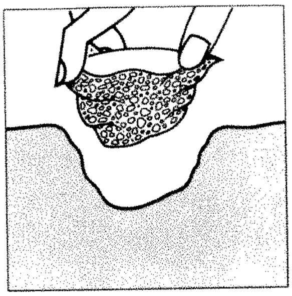

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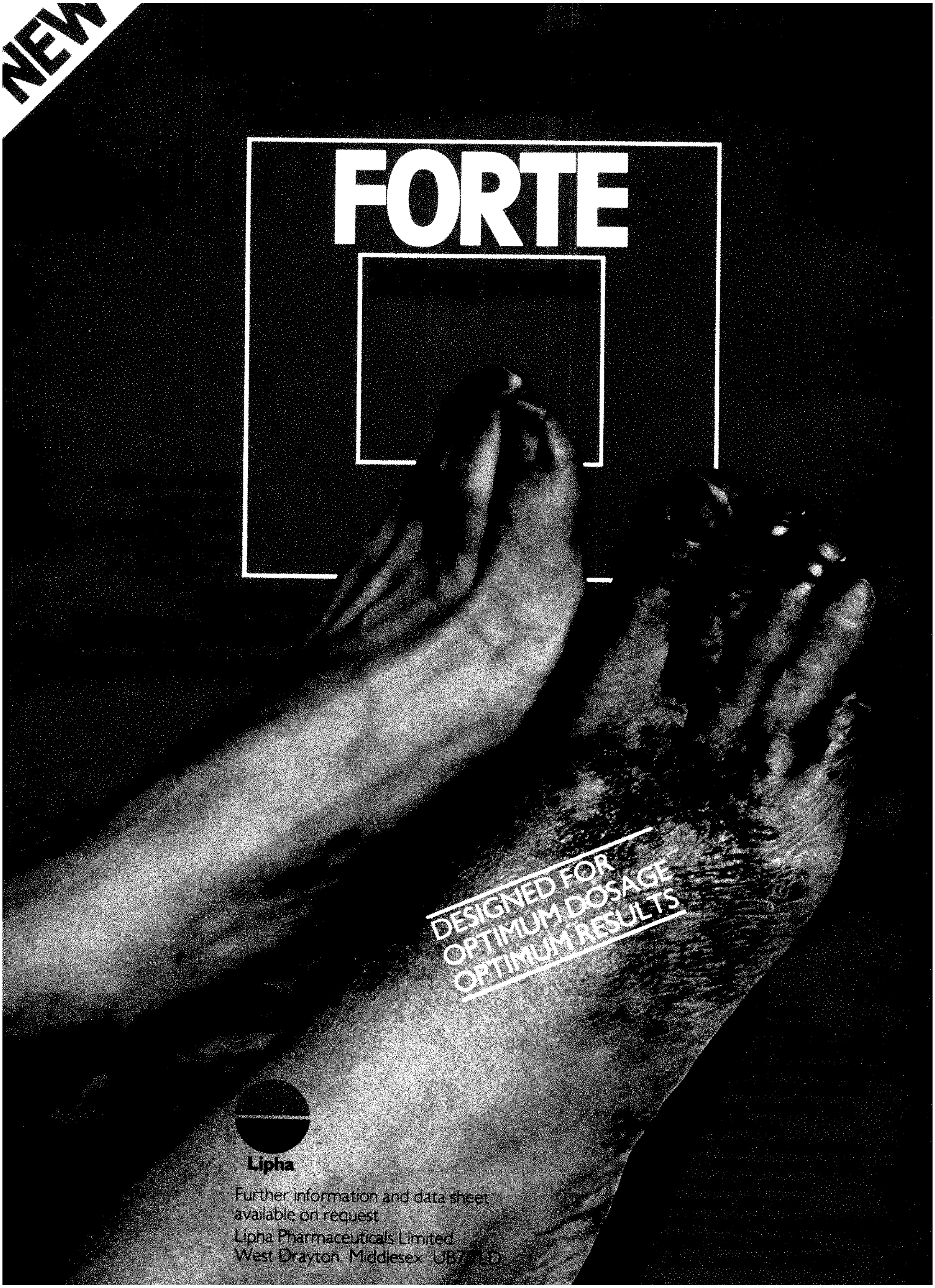

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Gastric reduction for morbid obesity: technique and indications

A. E. KARK AND M. BURKE*

SUMMARY

The results of gastric reduction for obesity in 12 patients are described. Emphasis is laid on preoperative weight loss, using jaw wiring in 9 patients. The successful outcome of the operation was found to depend on the formation of a small gastric pouch and a narrow gastro-jejunal anastomosis. A constant-sized pouch was achieved by forming the pouch around a 100-ml silicone balloon devised for the purpose. Postoperative results were good in 7 patients, partial success was achieved in 3 patients and there were 2 failures.

It is concluded that the procedure will produce successful results provided that a small proximal pouch with a narrow outlet is fashioned in motivated and psychologically well-balanced patients.

MORBID obesity is commonly defined as a body weight at least twice that predicted for a given height, but even an excess of adipose tissue of 40 kg is usually socially and physically disabling and potentially lethal. Many seriously overweight people require medical help and surgical intervention is increasingly being involved.

The currently popular surgical operation is one or other refinement of a small intestinal bypass procedure (Scott et al., 1971; Payne et al., 1973). However, in about half the patients, the consequences are marked metabolic disturbances, diarrhoea or hepatic dysfunction (Alden, 1977; Baddeley, 1977; Buckwalter, 1977). This is, for many, intolerable and is often unacceptable in terms of late mortality.

An alternative method which depends on mechanical reduction of stomach capacity has been pioneered by Mason (Mason and Ito, 1967; Mason et al., 1975) and is called gastric bypass. We have used this procedure, which we prefer to call gastric reduction, and present our experience of the past 4 years. The indications for its use and our modifications of the technique are described in detail.

Indications

Patients considered for operation are those who have been subjected to intensive investigation and prolonged medical treatment, in and out of hospital, but who regain weight. Before surgical intervention, patients must have undergone:

1. Thorough investigation which has excluded any endocrine cause of obesity.
2. Intensive controlled hospital and outpatient dietary regimens which have subsequently failed to maintain weight loss.
3. A period of teeth wiring with an 800 kcal liquid or soft diet maintained until the weight is steady and as close to ideal as can be achieved or, alternatively, for as long as the patient is able to tolerate this treatment.

The last requirement is necessary for three reasons. First, it tests determination and perseverance, thus selecting highly motivated patients, and eliminates the psychologically disturbed patient. Secondly, it ensures that gross obesity will have been substantially reduced, thus simplifying the operation and reducing post-operative morbidity. Thirdly, it allows time to explain to the patient the risks of the operation and the effects of the procedure.

Patients and methods

Operative technique

A long vertical midline incision is used from 2·5 cm above the xiphisternum to 5 cm below the umbilicus (*Fig.* 1). The xiphisternum is either removed or split. To form the proximal stomach pouch the upper third of the greater curvature is cleared of vasa brevia and attachments up to the hiatus and abdominal oesophagus (*Fig.* 1). It is essential to mobilize the upper greater curvature so that the high division of the stomach can be performed largely out of the abdomen and not in a relatively inaccessible, deep subdiaphragmatic cavity. The lesser curvature is exposed by making a two-finger opening in the lesser omentum about 6–8 cm from the hiatus, close to the gastric wall, without dividing vessels or vagi. Preservation of the right vagus is necessary to avoid retention in the large distal remnant, and the blood supply of the proximal remnant is ensured by the intact left gastric artery.

The proximal gastric pouch must not exceed 100 ml in capacity. The final size is difficult to estimate, and measurement by finger, eye or ruler along the curvatures is inaccurate and imprecise. This constant-sized proximal remnant is achieved by means of a sterilizable, silicone rubber, plastic sphere (Silgard 186, Dow Corning) (*Fig.* 2) which has a radius of 3·1 cm. The sphere, attached to a rigid 20-cm handle for ease of manipulation, is placed against the diaphragm over the outside of the upper stomach to outline the size of the pouch. The lesser and greater curvature just beyond the lower part of the sphere are picked up with Babcock's forceps and then the stomach is transected between soft clamps so that the upper pouch remains slightly larger than the sphere. The cut edges of

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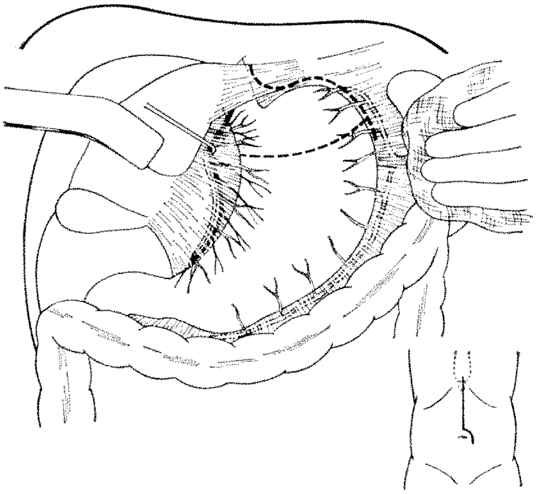

Fig. 1. Small proximal gastric pouch mobilized by division of vasa brevia and attachments right up to the abdominal oesophagus. Note: careful hand retraction of spleen; preservation of right vagus and left gastric artery arcade. *Inset*, Long upper midline incision extending from xiphisternum to below umbilicus.

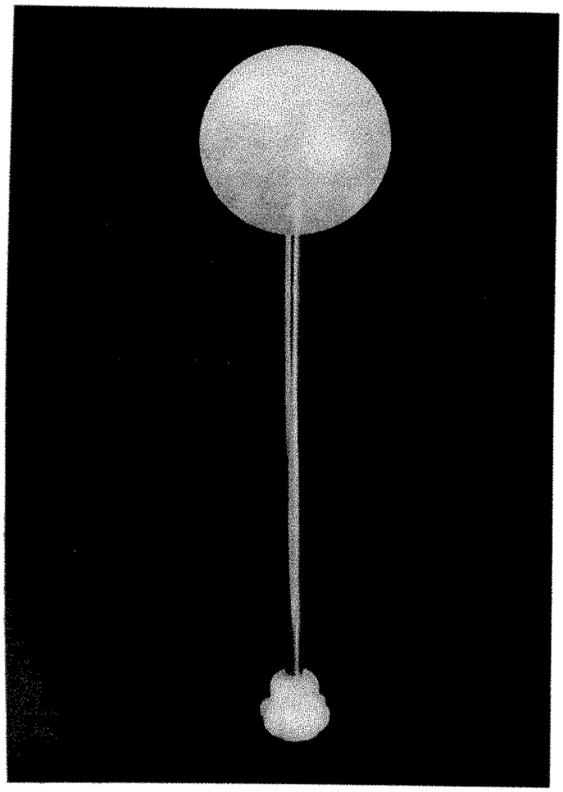

Fig. 2. Plastic sphere of volume 100 ml with rigid handle attached.

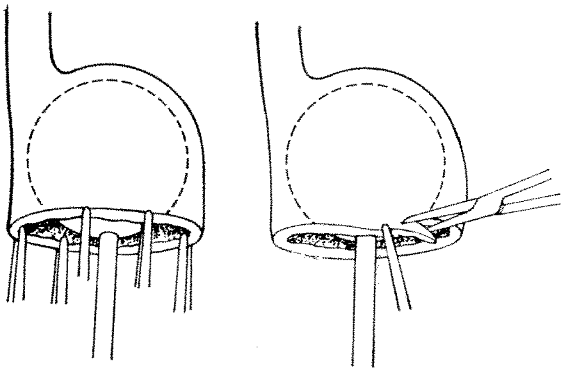

Fig. 3. Accurate assessment and tailoring of upper gastric pouch using a plastic sphere with a radius of 3·1 cm which provides a volume of about 100 ml. Note: trimming of redundant stomach wall so that closure can be snugly made around the sphere.

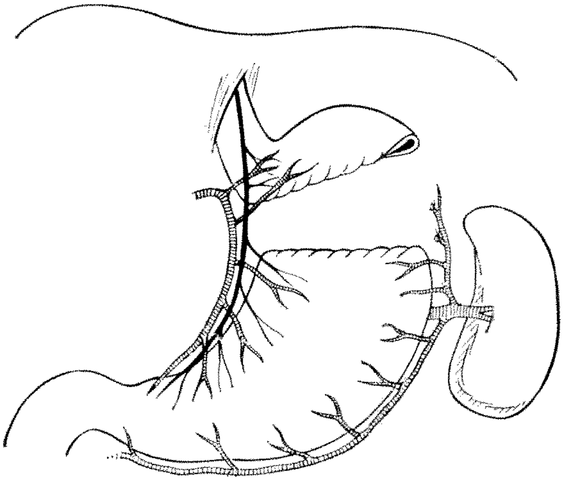

Fig. 4. Completed separation of upper gastric pouch with two-layer closure of all but a 12-mm opening measured by a 12-mm Hegar dilator.

the upper pouch are then picked up by a series of Allis forceps. The sphere is now inserted into the cavity of the upper pouch, pushed against the diaphragm and the lower rim pulled over the sphere (*Fig.* 3). The excess upper pouch is trimmed off so that the pouch, after suturing, will be of the same capacity as the sphere. The sphere is withdrawn and the pouch closed, leaving a small opening on the greater curvature just sufficient to admit a 12-mm Hegar dilator. Closure of the large distal stomach remnant is effected by standard inner continuous catgut and outer continuous silk sutures (*Fig.* 4).

Anastomosis of the proximal pouch to the jejunum is fashioned in the same way as a Polya–Hofmeister anastomosis using either a short retrocolic jejunal loop or an antecolic loop.

The size of the gastrojejunal stoma is critical. It must not be greater than 10 mm. The gastrojejunal stoma is therefore made with interrupted inner catgut and interrupted outer silk layers so as to minimize any further contraction of the opening during its construction. Before completing the inner layer, a Hegar dilator is inserted, and after being adjudged to fit snugly, the outer interrupted silk is placed (*Fig.* 5 inset). Next, the jejunum distal to the stoma is attached to the closed proximal pouch in the fashion of a Hofmeister valve. The distal stomach pouch is then tacked by three interrupted silk sutures to the anterior wall of the proximal segment, or to the diaphragm, so as to avoid possible rotation (*Fig.* 5).

If gallstones are present a cholecystectomy is performed. Drainage of the peritoneal cavity has not been necessary. Closure of the abdominal wall is effected by continuous monofilament nylon in one layer but the subcutaneous tissues and skin are left open with skin sutures in place for approximation after 4 days. The open wound is packed with Vaseline gauze and dry dressing.

A nasogastric tube is placed in the proximal gastric pouch, care being taken not to pass it through the stoma.

Patients

In the past 4 years 12 patients have been submitted to operation (*Table I*). Their ages ranged from 25 to 39 years except for one woman of 56 years accepted because of osteoarthritis of her hip. There were 7 women and 5 men. Nine patients were obese since childhood or early adolescence but 3 of the 7 women became obese after their first pregnancy and gained weight after each subsequent pregnancy.

All patients were socially embarrassed to a degree that caused them to remain housebound. Some were unemployable, 9 were dyspnoeic after walking short distances and 4 had marked orthopaedic deformities, mainly in the form of weight-bearing strain. All had a degree of psychological disturbance, 2 with episodes of depression requiring hospitalization. Six of the patients had severe domestic problems. Those who regained weight after gastroplasty and those who were treatment failures had recurrent domestic crises of a serious nature. All patients had undergone repeated dietary treatment with medical supervision. Jaw wiring was undertaken in 9 patients. Of the remaining 3 patients, 2 were unsuitable for wiring and 1 refused the procedure. The duration of the jaw wiring ranged from 2 to 24 months (2, 5, 5, 6, 6, 7, 9, 13, 14+10 months). In 3 patients the delay after jaw wiring before gastric reduction was undertaken was too long, and their weight increased in the intervening period from 76 to 106 kg, 71 to 105 kg and 101 to 117 kg respectively.

Patients did well in the postoperative period. One required immediate reopening for a suture line bleeding point. Three vomited in the first week until they became accustomed to the drastic limitation in intake. One patient started vomiting again 3 weeks after discharge but reassurance, fluids for 2 days and care with subsequent solids restored her to normal.

Seven of the 12 patients had a good result (*Table I*). Five of these are now close to or below their ideal weight and find little difficulty in maintaining this level. Two patients operated on more recently are both steadily losing weight, albeit slowly. None has experienced vomiting after the first few weeks and all are aware of their decreased stomach capacity. None has had metabolic problems. The haemoglobin and serum B12 levels have remained within normal limits. Dumping has not been encountered. Bowel action has been within normal limits (1–2 times a day, stools being firm). General health has been well maintained and, encouragingly, the domestic situations of the patients have stabilized.

Three patients may be regarded as partial successes: they still exhibit considerable social and psychological disturbance. Nevertheless, a year or more after the procedure they are substantially below their previous maximum weight. In one case the reduction was from 165 to 120 kg (ideal weight 86 kg), in the second the loss was from 138 to 113 kg (ideal weight 78 kg), while in the third patient the loss has been from 108 to 95 kg (ideal weight 64 kg). Thus, while still approximately 50 per cent above their ideal weight, they have lost enough to give them a subjective feeling of improvement.

Two patients were deemed failures. One, a young woman who had been obese from early childhood and who had undergone psychotherapy without success, had a gastroplasty in October 1974 when she weighed 103 kg. Although she reduced her weight to 95 kg she regained her preoperative weight within a matter of months and finally reached 119 kg, at which point—nearly 22 months later—she had the gastroplasty converted to a gastric reduction procedure. Her present weight is 110 kg, this being marginally less than her preoperative weight, but she is a determined and persistent eater. She had jaw wiring for 7 months prior to the first operation, losing 27 kg. She tolerated this manoeuvre, but, in retrospect, she

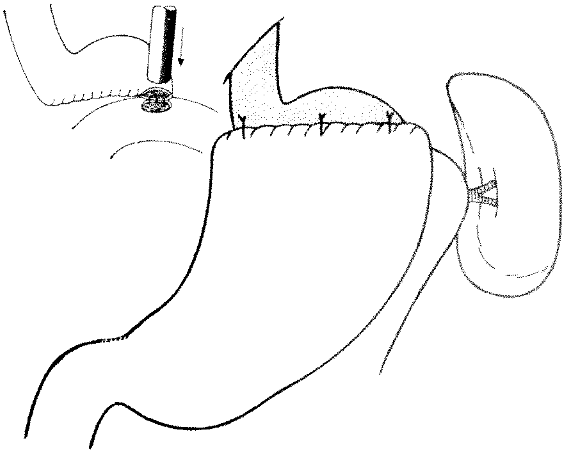

Fig. 5. The large distal pouch after closure by continuous inner catgut and continuous outer silk is finally attached by three to four interrupted silk sutures to the anterior surface of the upper pouch so as to avoid twisting. *Inset*, Accurate construction of the gastrojejunal anastomosis. Note: exactly the size of a 12-mm Hegar metal sound; *interrupted* catgut inner layer and *interrupted* silk outer layer.

Table I: RESULTS OF GASTRIC REDUCTION OPERATION

		Weight							
Sex	Age (yr)	Ideal	Presentation	After IMF	Time of IMF (mth)	Wt lost (kg)	Operation	Follow-up (mth)	Result
F	56	64	108	—	—	—	Plasty	52	Fair
F	28	61	115	76	7	17	Plasty Bypass	26	Poor
F	42	65	127	83	14 10	35 17	Plasty Bypass	5	Good
M	39	86	165	154	1½	11	Plasty	38	Fair
M	33	76	137	—	—		Plasty Bypass	21	Good
M	48	78	138	105	6	26	Bypass	26	Fair
F	30	62	100	68	6	34	Bypass	25	Good
F	35	63	99	74	13	27	Bypass	21	Good
F	34	58	96	59	16		Bypass	11	Good
M	25	75	119	72	10	47	Bypass Reconstr.	—	Died
F	30	68	132	—	—		Bypass	6	Good
M	32	93	207	—	—		Bypass	6	Good

IMF, Maxillomandibular fixation.

was so disturbed psychologically and so unstable in her domestic situation that she should not have been accepted for the surgical procedure.

The second failure was a young man of 26 who had gradually gained weight since late adolescence and who had made many unsuccessful attempts to diet both at home and in hospital. He agreed to jaw wiring, which was maintained for 9 months, during which time his weight fell from 119 to 71 kg. In June 1977 a gastric reduction operation was performed; however, on the third postoperative day, he demanded adamantly that the procedure be reversed. Despite persuasive medical advice, his insistence was acceded to, his weight as a result of retching and resistance to any food intake being 68 kg. The reversal procedure was technically satisfactory, but he developed peritonitis on the ninth postoperative day due to a leak at the suture line. After three subsequent operations he finally died.

Discussion

Only in the past decade has surgery been considered in the treatment of morbid obesity. The need has arisen because of the increasing numbers of obese people in Western society and their frequent referral to hospital for complications of their condition.

The more serious complications of gross obesity affect multiple organ systems and usually substantially lessen the life span. There is a very significant increase in the incidence of diabetes, hypertension and stasis ulceration (Buchwald et al., 1973). Orthopaedic problems usually affect hips, spine and knees, reflecting the abnormal weight carried by these joints; in older patients a moderate weight loss of about 24 kg can provide symptomatic relief.

Psychological problems are always present to a greater or lesser degree. There are few, if any, of these patients who have not had recurrent bouts of depression, and suicide attempts are not rare. It is important to exclude patients who have more serious manifestations, including overt psychoses, mental and social instability and unstable domestic situations.

People with moderate degrees of obesity often seek the help of dieting clubs. Only about a quarter of those who diet lose more than 9 kg, and fewer than 5 per cent lose as much as 18 kg. Drugs unfortunately can offer little, and cannot, at present, improve on the results of dietary control.

Because prolonged voluntary reduction of food intake in the obese will produce little if any long term weight loss (Bray et al., 1976), the use of maxillomandibular fixation has been evaluated (Rodgers et al., 1977; Fordyce et al., 1979). This extreme manoeuvre to limit calorie intake has proved technically feasible. In motivated patients it is acceptable and is a most effective method of achieving weight reduction.

We have used the interdental wiring method of maxillomandibular fixation (Fordyce et al., 1979) rather than metal cap splinting (Wood, 1977). Intensive dental care and continuing dental hygiene are necessary. Vomiting has not proved a problem and there has been no damage to the teeth or periodontal tissues. In our patients the average weight loss was 28·8 kg and the average duration of wiring was 8·6 months, results almost identical to those of Rodgers et al. (1977), who reported an average weight loss during 4–12 months' (8·5 ± s.d. 4·3) treatment of 29·3 kg (± s.d. 10·7 kg) in 17 patients. However, the relapse rate after unwiring is practically 90 per cent. Therefore, we have advised operation as soon as the patient begins to regain more than 3–4 kg above his/her best post-wiring weight.

The introduction of a small bowel bypass operation in 1963 and its subsequent modification has been followed by the recognition of the high incidence of late complications (O'Leary et al., 1974; Passaro et al., 1976; Wands et al., 1976; Alden, 1977; Baddeley, 1977, Buckwalter, 1977; Griffen et al., 1977; Parfitt et al., 1978). These, consisting of diarrhoea, fatty liver infiltration, renal stone, osteomalacia and polyarthritis, will in varying degrees affect nearly 50 per cent of patients. The extent of the ensuing morbidity constitutes in some surgeons' view a hazard sufficient to cause them to abandon the procedure (Alden, 1977; Buchwald, 1977; Griffen, 1977).

Although the weight loss produced by small bowel bypass is believed by some to be due to malabsorption of food (Mason et al., 1975), recent balance studies have shown that the main cause is reduced dietary intake (Woodward et al., 1975; Pilkington et al., 1976). Therefore, the alternative procedure of reducing the size of the stomach introduced by Mason (Mason and Ito, 1967), and with which he has extensive experience, appears promising. Recently Alden (1977) has modified the procedure by using an automatic stapling instrument for closure of the distal stomal pouch and for performing the gastrojejunal anastomosis. Both these manoeuvres substantially reduce the operating time. With this evidence and increasing support from other surgeons (Alden, 1977; Buckwalter, 1977; Gomez, 1979), we have adopted this principle in operating on a selected group of morbidly obese patients.

There are two methods of reducing the capacity of the stomach and therefore dietary intake. The first, a gastroplasty, consists of a nearly complete division of the stomach into an upper small segment and a lower larger one, the opening being the final 2 cm of undivided stomach. In 4 patients whom we have treated by gastroplasty there was an initial weight loss of 10–15 kg but after 6 months all of them had stabilized their weight at an insufficiently low level or had begun to regain weight. We have therefore abandoned this technique. However, Gomez (1979) has reintroduced this method using an automatic stapler without the need for division of the stomach, with a purse string of nylon around the newly fashioned stoma to prevent later enlargement. He has preferred this method in a series of 300 patients.

The second method, that of gastric reduction (or 'gastric bypass'), consists of a complete division of the stomach high in the fundus to separate a small proximal pouch from the remainder of the stomach which is left *in situ*.

It became clear early in this series that the procedure requires precision and that the margin of error in fashioning a reduced gastric pouch is small. If the size of the pouch is much smaller than 75–100 ml the first few months may well be intolerable, and even with some adaptation, later existence miserable. If the capacity is greater than 100 ml, even by a small amount, a pouch is left which accommodates very early to a large volume of food without patient discomfort.

In order to standardize the size of the upper pouch, the plastic sphere was introduced. Even this is not without error, since the capacity of the stomach is determined not only by a varying amount of stretch of the gastric wall but also by motility and emptying time of the pylorus. Thus, the size of the stoma is important. It must be small so that determined eating is prevented not only by the size but also by slow emptying. On the other hand, it must not be less than 8 mm otherwise partial obstruction and persistent vomiting will occur. As there is always some late contraction by 10–20 per cent, it is important to limit the narrowing of the stoma during construction by means of carefully placed interrupted inner and interrupted outer sutures. There should be not more than six sutures on both the anterior and posterior surfaces, each suture being about 2 mm apart. Early X-ray studies before leaving hospital show that a narrow 4–6 mm opening due to postoperative oedema is present. After some weeks this widens to about 10 mm.

After 6–12 months the new small stomach learns to adapt to small, well-spaced meals and the major bar to continuous nibbling and snacks is the rapid feeling of fullness that patients learn to dislike. Regular exercise on a daily basis must be insisted upon as a part of the postoperative therapy. High protein diets should be prescribed.

Long term results reported by Mason et al. (1975) can be summarized as a weight loss of 50 kg or more in one-third of patients, 25–50 kg in a further third and less than 25 kg in the remaining third. The average weight loss at 5 years is approximately 36 kg. In both Alden's (1977) and Buckwalter's (1977) series—each being a comparative study of the effects of intestinal and gastric bypass—weight loss was achieved at about the same rate, although the loss is greater and more predictable after gastric bypass. After both procedures at least 75 per cent of excess weight will be lost within 2 years and the younger and more active the patient, the greater the loss. However, it is possible to 'outeat' a gastric bypass by determined drinking of high calorie drinks, whereas this cannot be achieved after jejunoileal bypass. The weight loss is maximal during the first 6 postoperative months (10–20 kg) with a further loss of 5–10 kg up to the first year (Mason et al., 1975). Thereafter there is usually a slight further loss or the weight stabilizes. Thus, in general a loss of at least 75 per cent of excess weight can be expected in the first 2 years.

In a series of nearly 400 gastric bypass operations (Printen and Mason, 1977) a 2·8 per cent operative mortality was reported. This includes patients over the age of 50, in whom the mortality rate is four times higher than in those under 50. Recent series report even lower mortality rates, comparable at least to those following jejunoileal bypass (Alden, 1977; Buckwalter, 1977; Griffen, 1977; Gomez, 1979).

Despite the theoretical risk of producing a situation conducive to stomal ulceration, a stomal ulcer rate of only 1·8 per cent has been reported (Mason et al., 1978). No metabolic or nutritional deficiencies have been documented either in other series or in our group of 12 patients. Particularly gratifying has been the stable gastrointestinal function with no late vomiting or dumping and normal stool frequency and consistency. Thus, there is increasingly good evidence that surgical intervention in carefully selected patients is justifiable and, in most patients, beneficial. Longer follow-up studies are required to determine that the weight remains stable and that there are no late complications.

References

ALDEN J. F. (1977) Gastric and jejunoileal bypass. *Arch. Surg.* **112**, 799–806.

BADDELEY M. (1977) Jejunoileal bypass for obesity. *Br. Med. J.* **2**, 640.

BRAY G. A., BARRY R. E., BENFIELD J. R. et al. (1976) Intestinal bypass surgery for obesity decreases food intake and taste preferences. *Am. J. Clin. Nutr.* **29**, 779–783.

BUCHWALD H., LOBE R. and VARCO R. L. (1974) Liver biopsy findings in 77 consecutive patients undergoing jejunoileal bypass for morbid obesity. *Am. J. Surg.* **127**, 48–52.

BUCHWALD H., SCHWARTZ M. Z. and VARCO R. L. (1973) Surgical treatment of obesity. *Adv. Surg.* **7**, 235–259.

BUCKWALTER J. (1977) Prospective comparison of the jejunoileal and gastric bypass operations for morbid obesity. *World J. Surg.* **1**, 757–768.

FORDYCE G. L., GARROW J. S., KARK A. E. et al. (1979) Jaw wiring and gastric bypass in treatment of severe obesity. *Obesity Bariatric Med.* **8**, 14–17.

GOMEZ C. (1979) *Am. J. Clin. Nutr.* (In the press.)

GRIFFEN W. C., YOUNG L. and STEVENSEN C. C. (1977) Prospective comparison of gastric and jejuno-ileal bypass procedures for morbid obesity. *Ann. Surg.* **186**, 500–509.

MASON E. E. and ITO C. (1967) Gastric bypass. *Surg. Clin. North Am.* **47**, 1345–1349.

MASON E. E., PRINTEN K. J., BLOOMERS T. J. et al. (1978) Gastric bypass for obesity after ten years' experience. *Int. J. Obesity* **2**, 197–206.

MASON E. E., PRINTEN K. J., HARTFORD C. E. et al. (1975) Optimizing results of gastric bypass. *Ann. Surg.* **182**, 405–414.

O'LEARY J. P., THOMAS W. C. and WOODWARD E. R. (1974) Urinary tract stone after small bowel bypass for morbid obesity. *Am. J. Surg.* **127**, 142–147.

PARFITT A. M., MILLER M. J., FRAME B. et al. (1978) Metabolic bone disease after intestinal bypass for treatment of obesity. *Ann. Intern. Med.* **89**, 193–199.

PASSARO E., DRENICK E. and WILSON S. E. (1976) Bypass enteritis. *Am. J. Surg.* **131**, 169–174.

PAYNE J. H., DEWIND L. T., SCHWAB C. E. et al. (1973) Surgical treatment of morbid obesity. *Arch. Surg.* **106**, 432–437.

PILKINGTON T. R. E., GAZET J. C., AUG L. et al. (1976) Explanation for weight loss after ileojejunal bypass in gross obesity. *Br. Med. J.* **1**, 1504–1505.

PRINTEN K. J. and MASON E. E. (1977) Gastric bypass for morbid obesity in patients more than 50 years of age. *Surg. Gynecol. Obstet.* **144**, 192–194.

RODGERS S., GOSS A., GOLDUCY R. et al. (1977) Jaw wiring in treatment of obesity. *Lancet* **1**, 1221–1225.

SCOTT H. W. JUN., SANDSTEAD H. H., BRILL A. B. et al. (1971) Experience with a new technique of intestinal bypass in the treatment of morbid obesity. *Ann. Surg.* **174**, 560–572.

WANDS J. R., LA MONT J. T., MANN E. et al. (1976) Arthritis associated with intestinal bypass procedure for morbid obesity. *N. Engl. J. Med.* **294**, 121–124.

WOOD G. B. (1977) Early results of treatment of the obese by a diet regimen enforced by maxillo-mandibular fixation. *J. Oral Surg.* **35**, 461–466.

WOODWARD E. R., PAYNE J. H., SALMON P. A. et al. (1975) Morbid obesity. *Arch. Surg.* **110**, 1140–1445.

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Hepatic resection for trauma, tumour and biliary obstruction

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SUMMARY

Hepatic resection was performed in 37 patients. Fifteen emergency procedures were undertaken for blunt trauma and 16 patients had elective resection for hepatic tumour. A further 6 resections were performed for benign biliary tract obstruction. The importance of preoperative assessment and the indications for resection are discussed particularly in relation to resection for biliary obstruction. Operative procedures are outlined and the technique of extended left lobectomy is described in detail.

THE detailed anatomical studies of McIndoe and Counsellor (1927), Healey (1954), Goldsmith and Woodburne (1957) and others formed the basis for technical developments in liver surgery and have resulted in the precise documentation of the formal operations involving partial hepatectomy. Liver resection has thus become more widely used in the treatment of hepatic disorders, although the indications for partial hepatectomy in certain conditions are still a matter for debate. The place of hepatic resection in injury has become more clearly defined (Walt, 1978), but its value in tumours of the liver and bile ducts is still being determined. Resection is used only infrequently in benign biliary obstruction.

This paper reports a consecutive series of patients submitted to hepatic resection. The indications for surgery and management of patients requiring resection for blunt liver trauma, tumour and biliary obstruction are discussed.

Preoperative considerations

Diagnosis and assessment

Trauma: In patients who have sustained blunt abdominal trauma, awareness of possible liver damage and astute clinical judgement are important. Classic signs of intra-abdominal injury may be present, but in some cases of extensive liver injury shock is often not a presenting feature and there may be minimal physical signs (Walt, 1969; Vajrabukka et al., 1975). The presence of fractured ribs and, in addition, fractures of the right upper limb is common (Vajrabukka et al., 1975). In this series abdominal paracentesis was not employed and peritoneal lavage only rarely. Emphasis was placed on careful observation and repeated examination, laparotomy being performed on suspicion (Bolton et al., 1973).

Special methods of investigation including ultrasound, isotope scanning and selective coeliac axis angiography were only used in patients presenting in a less acute manner. In all patients a baseline coagulation screen was obtained, if possible before transfusion was commenced (Vajrabukka et al., 1975).

Tumour and biliary tract obstruction: In the selection of patients for elective liver resection for tumour or biliary tract obstruction extensive investigations are essential for accurate preoperative assessment.

In patients presenting with biliary tract obstruction, whether benign or malignant, a combination of grey scale ultrasound, fine needle percutaneous transhepatic cholangiography (PTC) (*Fig.* 1) and endoscopic retrograde choledochopancreatography (ERCP) was used in an ordered manner (Benjamin et al., 1978; Blumgart, 1978) to define precisely the anatomical location, extent and nature of the obstruction present.

Diagnosis of liver tumour was based on the history, physical examination, serological tests, isotope and ultrasound scanning and selective hepatic arteriography. A target liver biopsy was obtained using a Tru-cut needle under direct laparoscopic control. This technique provided visualization of the extent of tumour spread and gave an assessment of operability. Patients with hepatic and bile duct tumours were screened for extrahepatic deposits, using a combination of chest X-ray, skeletal survey and/or isotopic bone scan. Patients with secondary tumours in the liver arising from colonic primary sites also underwent barium enema or colonoscopic examination.

Selective arteriography and splenoportography were reserved for patients in whom it was considered that resection might be feasible. These two investigations demonstrated not only the presence of tumour but, importantly, the anatomy to be encountered at operation (*Fig.* 2). In particular, assessment of the involvement of vessels at the porta hepatis is essential in planning operative approaches. Inferior venacavography and hepatic venography were also performed to assess the extent of tumour involvement in these structures.

Tumours were considered irresectable in the presence of multiple deposits in both lobes of the liver and in patients with involvement of extrahepatic structures or radiological evidence of invasion (*Fig.* 3), but not compression (*Fig.* 4) of the inferior vena cava. Likewise, occlusion of both (but not one) branches of the portal vein was taken as an index of inoperability.

The general condition of the patients was assessed carefully and special attention was paid to the pathophysiological effects of jaundice (Blumgart, 1978), to the presence or absence of coagulation defects and to the assessment of renal function (Dawson, 1965; Allison et al., 1978).

Prophylactic antibiotics were used in patients with biliary tract obstruction because an increased incidence of biliary infection is known to occur in these cases (Flemma et al., 1967; Keighley, 1977; Shingleton, 1977).

Operative techniques

The incision used depended upon circumstances. Exploration for liver injury was initially performed through a right upper paramedian rectus-splitting incision or a midline incision. This was extended as a thoracoabdominal incision, either through the seventh interspace with incision of the diaphragm towards the vena cava, or more recently by means of a median sternotomy (Miller, 1972). This latter approach is rapid, spares disruption of either pleural cavity and gives good access to the major hepatic veins and the intracardiac inferior vena cava. Should the diaphragm require to be split, this can be done through the central tendon. Laparotomy for tumour was through either a bilateral oblique 'roof-top' incision or a thoracoabdominal incision similar to that used in cases of trauma.

Formal hepatic lobectomy either in the emergency or elective situation was preceded by isolation of the vascular and biliary structures of the porta hepatis. The vessels and ducts supplying the segment to be excised were then ligated and divided. For tumours involving the porta hepatis we have employed a 'liver-split' technique (Templeton and Dodd, 1963; Waddell, 1967). The liver substance is divided in the plane just to the left of the gallbladder fissure using a finger fracture technique and deepening the incision of the liver substance posteriorly in a slightly oblique direction towards the vena cava. This initial hepatotomy (*Fig.* 5) allows intrahepatic evaluation without committing the surgeon to resection. Final assessment of operability is made and if it is decided to proceed

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with lobectomy then the appropriate vessels can be divided (*vide infra*).

Liver tissue was sectioned using a combination of incision, diathermy and the finger fracture dissection technique (Foster and Berman, 1977). The hepatic veins were frequently approached from within the liver substance, especially in resection for trauma (Blumgart and Vajrabukka, 1972). In patients with large tumours extending close to the vena cava, formal dissection of the hepatic veins was carefully carried out from below upwards, thus allowing the liver substance to be lifted free from the vena cava. Large quantities of liver parenchyma were never compressed but it was found that absorbable liver buffers (Wood, Capperauld et al., 1976) allowed gentle compression of liver tissue with efficient haemostasis.

Choledochotomy and T tube drainage was used in all but 3 patients undergoing right hepatic lobectomy or extended right hepatic lobectomy for trauma but not in resection carried out for tumour. In patients with biliary tract obstruction requiring removal of a portion of the biliary ductal apparatus reconstruction was always over a transhepatic or transjejunal tube in order to splint the anastomosis (Benjamin and Blumgart, 1979). Postoperative drainage was used in all patients.

Hepatic resection

Right hepatic lobectomy and extended right hepatic lobectomy (trisegmentectomy) were performed by standard methods (Balasegaram, 1970; Longmire et al., 1974; Ong and Lee, 1975; Starzl et al., 1975; Adson and Beart, 1977; Ong, 1977). In one patient submitted to trisegmentectomy for primary hepatoma, invasion and complete occlusion of the right branch of the portal vein was demonstrated by splenoportography. Adequate exposure at the porta hepatis allowed excision of a segment of portal vein at its bifurcation with direct suture repair (*Fig*. 2).

Left lobectomy was likewise performed by standard methods and left lateral segmentectomy using the clamp described by Storm and Longmire (1971). Liver buffers (Wood, Capperauld et al., 1976) were placed before the clamp was released in order to control haemorrhage.

Extended left hepatectomy: In 2 patients resection of liver tissue involved removal of the entire left lobe of the liver, the quadrate and caudate lobes and a portion of the right lobe. We refer to this procedure as extended left hepatectomy. In both instances the operation was necessitated by tumour involving the hilar structures, mainly on the left side.

The approach varies subtly from that adopted in carrying out the formal operations of right or left hepatectomy in which the aim is to devascularize that portion of the liver to be removed. In patients with tumour involving the hilus, the important objective of maintaining a vascular supply, venous effluent and biliary drainage to the remaining non-diseased segment must be specially borne in mind throughout the dissection. The structures feeding the porta hepatis should initially be isolated so that control can readily be obtained when necessary. The liver is then split, as described above, just to the left of the gallbladder fossa, deepening the incision posteriorly to skirt the right margin of the tumour with adequate clearance. As this incision is deepened it becomes easier to assess resectability. In both patients in whom this approach was employed the course of the right branch of the portal vein and associated arterial and biliary structures was clearly seen and the antero-inferior and posterior segmental branches of the portal triad were preserved. During the dissection the middle hepatic vein and left hepatic vein were either ligated separately or, if the middle hepatic vein drained into the left, this was dealt with alone. The right hepatic vein lies further back between anterior and posterior segments of the right lobe of the liver and should have been demonstrated preoperatively by hepatic venography to be clear of tumour.

In the 2 patients in whom this approach was used, selective arteriography and splenoportography had revealed the arterial supply to the right lobe of the liver to be free from tumour involvement but the left branch of the portal vein was occluded in each instance (*Fig*. 6). In both cases there proved to be involvement of the bile duct at the confluence by tumour invasion.

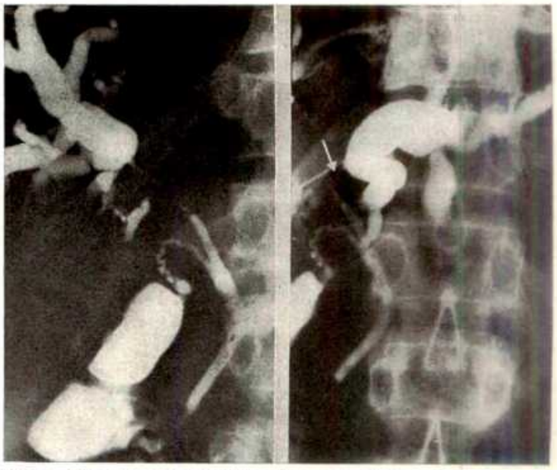


Fig. 1. Percutaneous transhepatic cholangiograms demonstrating both the right and the left (arrowed) intrahepatic ductal system of the liver in a 50-year-old man with a 1-month history of painless obstructive jaundice. The cholangiogram performed via the right lobe of the liver shows obstruction of the right hepatic duct by a carcinoma which extends to the common hepatic duct. The PTC performed via the left lobe shows obstruction to the main left hepatic duct (arrowed) but, in addition, there is an accessory duct opening into the common hepatic duct. The main left hepatic ductal system is grossly dilated.

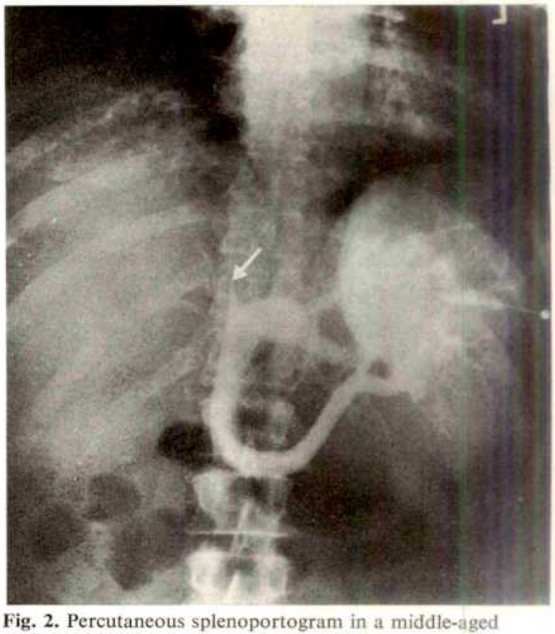


Fig. 2. Percutaneous splenoportogram in a middle-aged patient with a large primary hepatocellular carcinoma occupying the entire right lobe of the liver. Note displacement of the main trunk of the portal vein with occlusion of its right main branch (arrowed). The left branch of the portal vein is intact. Knowledge of such portal venous involvement is vital during operation, particularly during dissection at the hilus of the liver.

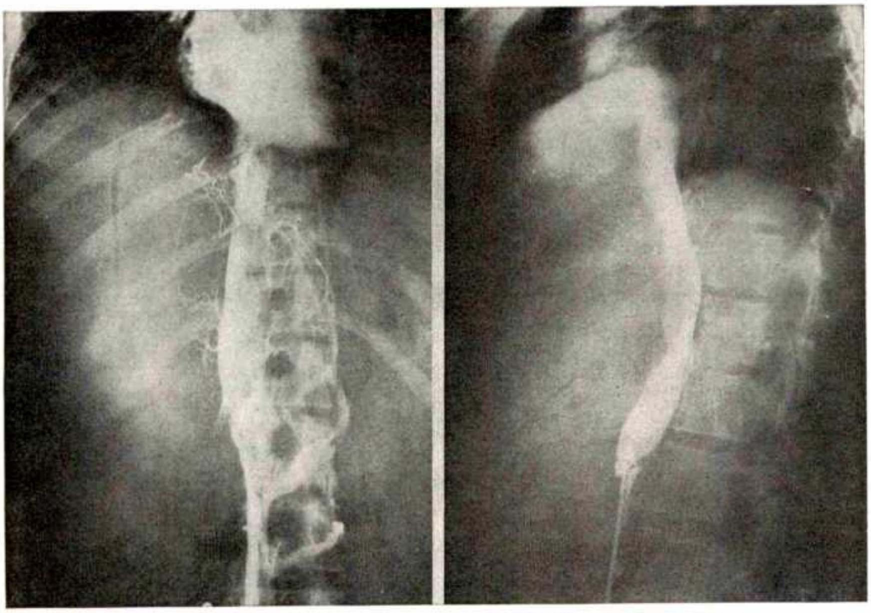


Fig. 3. Inferior venacavography, both in the anteroposterior and lateral views, in a 19-year-old patient with a primary hepatocellular carcinoma. There is invasion of the inferior vena cava seen as filling defects in both projections and collateral circulation reflecting partial obstruction. This must be differentiated from the appearances shown in *Fig*. 4.

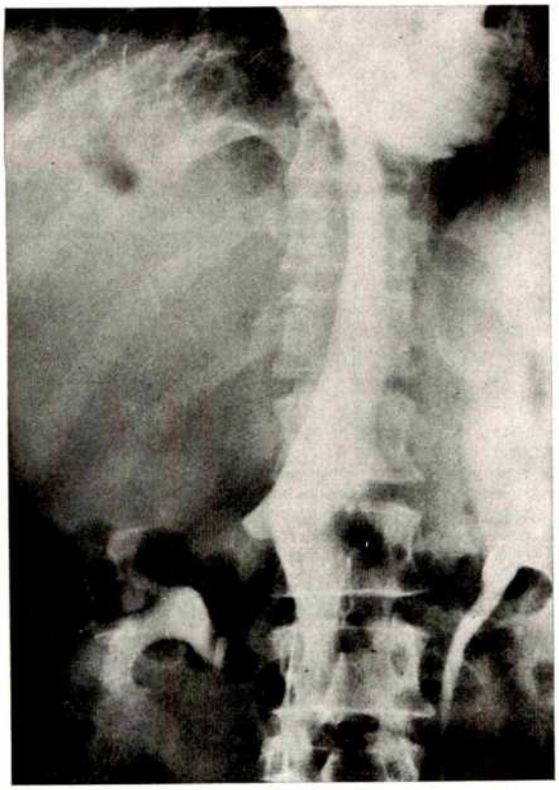


Fig. 4. Inferior venacavogram in a 54-year-old man with primary hepatocellular carcinoma involving the right lobe of the liver. There is compression but not invasion of the inferior vena cava. (Same case as in *Fig*. 2.)

J. B., a 51-year-old male, presented with painless obstructive jaundice. PTC and ERCP demonstrated a complete block at the common hepatic duct bifurcation. Aspiration of bile at ERCP established the diagnosis of malignancy. Selective hepatic arteriography was normal but splenoportography revealed that the left branch of the portal vein was almost totally occluded (*Fig*. 6).

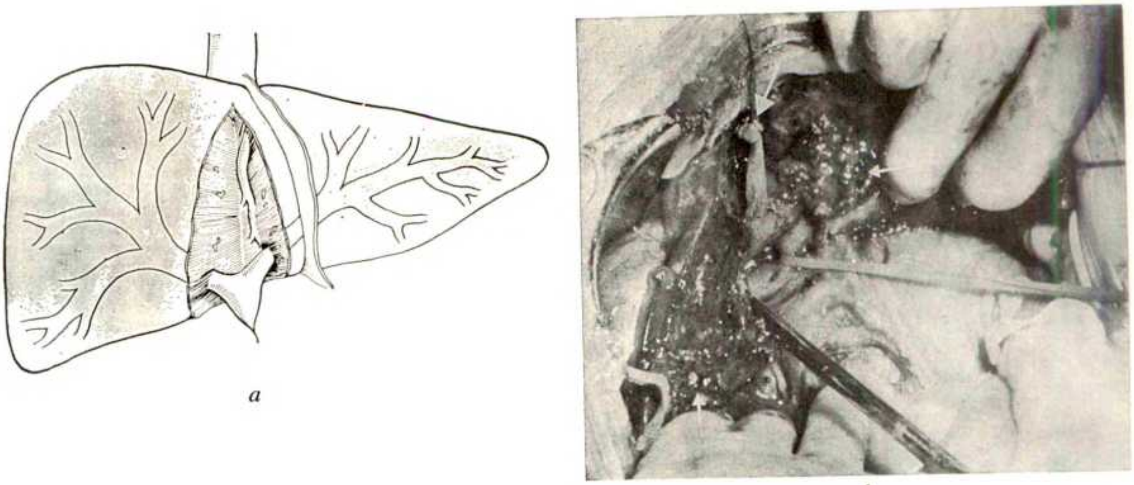
The feasibility of liver resection could not be assessed until hepatotomy was performed. The liver was finger fractured in the vascular plane and branches of the middle hepatic vein ligated. The confluence of the bile ducts was displayed showing considerable extension of tumour to the left and posteriorly as well as into the right lobe for a short distance. The supraduodenal common bile duct was transected and turned upwards (*Fig*. 5). The portal vein was isolated below its bifurcation and its right branch was dissected upwards into the liver.

The left portal vein was transected at its origin and the defect closed by direct suture. The tumour was traced into the right lobe of the liver and clearance obtained, the right intrahepatic ducts being sectioned and three separate branches identified to be clear of tumour. The left lobe of the liver was mobilized and the left hepatic vein divided. The caudate lobe was mobilized from the vena cava by serial dissection of the minor hepatic veins from below upwards and the entire left lobe, caudate lobe, quadrate lobe and a segment of the right lobe removed *en masse*.

A Roux-en-Y loop of jejunum was fashioned and three separate hepaticojejunostomy anastomoses made, each being splinted (two by means of transhepatic tubes and one via a transjejunal tube).

Histology of the specimen confirmed the presence of a cholangiocarcinoma extending well into the caudate lobe and left lobe of the liver. The excision edge was clear of tumour.

A. J., a 16-year-old female, presented with a 2-week history of right upper quadrant pain, jaundice and one episode of haematemesis. There was a previous history of oral contraceptive ingestion. Alphafetoprotein estimation was negative. PTC showed gross dilatation of the right intrahepatic bile ducts and the common bile duct. The left hepatic duct was not outlined. Laparotomy revealed a mass in the porta hepatis


a

b

Fig. 5. *a*, The performance of a 'liver split' procedure in a patient with benign bile duct stricture. Note that the incision in the liver substance is made several centimetres to the right of the ligamentum teres and just to the left of the gallbladder fossa (gallbladder removed in this instance). The incision in the liver substance is just to the right of the middle hepatic vein which is shown in the depth of the hepatotomy. *b*, The operative field in a 51-year-old man with carcinoma involving the confluence of the bile ducts and extending well into the left branch of the portal vein (*see Fig*. 6). A 'liver split' has been performed and the right and left lobes of the liver are seen separated by the operator's fingers (small arrows). The common bile duct has been transected above the duodenum and turned upwards into the liver split (large arrow). The portal vein is clearly seen in the depth of the hepatotomy and its left branch has a sling at the orifice, the vein clearly being implicated by the tumour in the left hepatic duct. The hepatic artery has been dissected and is evident below the portal vein.

involving mainly the left side but extending also into the right and caudate lobes. Choledochotomy was performed and loose tumour removed which proved to be hepatocellular carcinoma. A tube was left in the common hepatic duct and the abdomen was closed. The patient was then referred to Glasgow Royal Infirmary. Selective hepatic arteriography revealed the left hepatic artery arising from the left gastric artery and supplying a large tumour mass in the area of the porta hepatis. The right hepatic artery arose from the superior mesenteric artery and appeared to be clear of the tumour and not involved in its blood supply. Splenoportography showed complete occlusion of the left branch of the portal vein. At subsequent exploration the enlarged common bile duct was completely transected and loose tumour withdrawn. The tumour did not invade the wall of the main duct but the orifice of the left hepatic duct was completely occluded. The upper portion of the common hepatic duct was turned upwards and a segment of its wall excised at the junction of the left hepatic duct, the defect created being closed by direct suture.

The liver was then split to the left of the gallbladder fossa, the incision being deepened so as to skirt the right margin of the tumour. Dissection of the portal vein, removal of the orifice of the left portal vein and subsequent repair of the defect was similar to that in the previous case. The left hepatic artery was ligated and the left lobe of the liver mobilized. The caudate lobe was dissected free from the inferior vena cava and the operation completed by division of the left hepatic vein. Continuity of the common bile duct was restored by end-to-end anastomosis, and splinted by a transhepatic tube passed through the right lobe of the liver.

Both these patients made an excellent recovery from operation.

Results

A total of 37 hepatic resections has been carried out (*Table I*). The age range of the patients was from 9 to 59 years. There was 1 immediate postoperative death (defined as death during or within 24 h of operation) and 4 further patients died before leaving hospital.

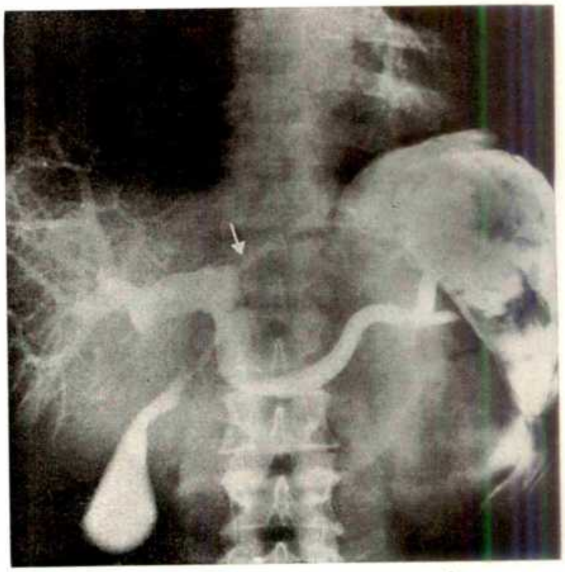


Fig. 6. Splenoportography showing almost complete occlusion of the left branch of the portal vein (arrowed). This patient (same case as in *Fig*. 5) presented with a 2-week history of painless obstructive jaundice and was found on PTC and ERCP to have a cholangiocarcinoma at the confluence of the bile ducts involving the main trunk of the right hepatic duct and extending well into the left lobe of the liver. The X-ray shows the right branch of the portal vein free of tumour and similarly selective hepatic arteriography had shown the right hepatic artery to be clear of tumour. There is contrast medium in the gallbladder from ERCP carried out a day earlier.

Table I: PATIENTS AND SURVIVAL FOLLOWING HEPATIC RESECTION

Group	No. of patients	Hospital mortality	Overall survival	Survival period before death	Follow-up period of survivors
Trauma	15	3 (20%)	12 (80%)	10 h–10 d	12 mth–12 yr
Tumour	16	2 (12·5%)	6 (37·5%)	8 d–4½ yr	5 mth–6 yr
Primary	7	1 (14·2%)	4 (57%)	12 d–2 yr	5 mth–2 yr
Secondary	9	1 (11%)	2 (22%)	5 mth–4½ yr	26 mth–7 yr
Biliary obstruction	6	0	6 (100%)	—	11 mth–5½ yr

Eight other patients have died of cancer during follow-up at periods varying from 5 months to 4½ years. All the patients surviving liver resection for liver injury or for benign biliary obstruction remain alive and well.

Trauma

Fifteen patients (age range 9–39 years) were submitted to emergency resection for hepatic trauma. Twelve patients underwent right lobectomy while 2 had extensive resectional débridement and suture and 1 had left lateral segmentectomy. Three patients died, 2 of associated head and chest injuries and 1 with associated injuries and concomitant post-traumatic pancreatitis and renal failure. In each instance hepatic resection controlled haemorrhage and biliary leakage.

The first 8 patients have been described in detail (Vajrabukka et al., 1975). All 7 patients treated since then have survived and all 12 survivors are alive and well at periods ranging from 6 months to 13 years after operation.

Tumour

Sixteen patients (age range 16–59 years) underwent hepatic resection for tumour. Seven patients had primary tumour of the liver or biliary system; trisegmentectomy was performed in 4 patients and extended left hepatic lobectomy in 2 patients with primary hepatocellular carcinoma, cholangiocarcinoma or gallbladder carcinoma. In 1 patient a left lateral segmentectomy was performed for an intrahepatic haemangioma. In 3 patients tumour involvement of the portal vein was noted.

Nine patients had resection of secondary hepatic deposits, the primary tumour sites being colon or rectum in 6, small intestinal carcinoid in 2 and hypernephroma in 1 patient. One right hepatic lobectomy, 3 trisegmentectomies, 2 lateral segmentectomies and 3 wedge excisions were performed in these patients.

Six patients (37·5 per cent) are alive, one of whom has recurrent cholangiocarcinoma, the period of follow-up being from 5 months to 7 years. Two patients with primary liver tumours died 18 months and 2 years respectively after resection. Of the 9 patients with secondary tumours, 6 died between 5 months and 4½ years after surgery.

Two patients died in the postoperative period (12·5 per cent). Both patients died from haemorrhage. The first patient, a 38-year-old woman, had a left hemicolectomy for splenic flexure carcinoma and was noted to have a 2-cm metastatic deposit in the right lobe of the liver. Eighteen months later, when she was referred for hepatic resection, the solitary nodule was 8 cm in diameter and close to the hilus. Tumour was found to be involving the right branch of the portal vein and the origin of the left branch. Trisegmentectomy was performed, during which procedure the portal supply to the left lobe was compromised and the patient died 8 days later from haemorrhage caused by an irreversible coagulation defect. On the basis of this experience we now perform splenoportography in all patients with potentially resectable tumours close to the hilus of the liver.

A further patient died with uncontrollable haemorrhage from gastric erosions 12 days postoperatively. It is now our policy to give prophylactic cimetidine to all jaundiced patients undergoing resection.

In addition to the possible curative role of hepatic surgery for tumour, several patients have had complete relief of symptoms following palliative resection of the primary or secondary hepatic lesion. One patient suffering considerable right hypochondrial pain and jaundice was afforded excellent symptomatic relief for 15 months before developing bone metastases.

Benign biliary obstruction

Six patients (age range 26–58 years) have been submitted to hepatic resection for benign bile duct stricture. There was no hospital mortality and all patients are alive and well at periods ranging from 11 months to 5½ years.

The operations carried out were left lobectomy with intrahepatic hepaticojejunostomy for 1 patient with a high bile duct stricture following liver injury for which right hepatic lobectomy had previously been performed; right hepatic lobectomy with intrahepaticojejunostomy in 1 patient with iatrogenic high bile duct stricture and quadrate lobectomy was performed in 4 patients for iatrogenic bile duct stricture.

Postoperative progress

All cases involving major hepatic resection were nursed initially in an intensive care unit, the patients spending 24 h on intermittent positive pressure ventilation as a routine. The main immediate dangers occurring after hepatic resection are, first, coagulation defects due to large volumes of transfused blood and diminished production of hepatic clotting factors and, secondly, hypoglycaemia following depletion of glycogen stores.

Impairments of blood clotting were reversed with the use of fresh frozen plasma, fresh blood and platelet transfusion. An irreversible coagulation defect occurred only in the patient with liver failure consequent on hepatic necrosis of the remaining liver segment. Blood sugar was monitored regularly, particularly during the first 48 h postoperatively and only 1 patient required 50 per cent dextrose infusions.

The only other major postoperative complication was subphrenic abscess which developed in 3 patients and in 1 this was complicated by penetration of the diaphragm by the abscess with the development of a right-sided empyema.

Wound infection necessitating drainage of the wound developed in 3 further patients.

Following hepatic resection there was a transient rise in ALT and alkaline phosphatase levels and all the patients were jaundiced to a variable degree. The total serum protein levels fell, this being mainly due to a fall in the albumin fraction, reaching a nadir of 2·3–2·5 g/l at about 2 weeks after surgery. In some patients albumin supplementation to a total of 100 g/day was given but this did not appear to affect the speed at which the proteins returned to normal, this usually occurring by the sixth to seventh postoperative week.

Discussion

Hepatic resection is a major operation and the indications for its use require careful assessment. The mortality and morbidity are considerable and resectional methods should not be employed where more simple methods will suffice. On the other hand, it is important to realize that in some situations less radical approaches have no chance of success.

The indications for resection are becoming more clearly defined, although fine judgement is required at the time of operation. Major shattering wounds of the liver cannot be sutured and while temporary packing may be of value and allow transport of the patient to a centre where resection can be performed (Calne et al., 1979; Walt, 1978), it is generally contraindicated and is associated with a high incidence of secondary haemorrhage, infection and biliary leakage.

Dramatic arrest of bleeding can follow arterial ligation and in some circumstances this may be safely carried out (Aaron et al., 1975). The portal circulation is adequate to provide liver nourishment and the liver deprived of its arterial supply readily develops a collateral circulation. However, vascular ligation to a segment of the liver may not control haemorrhage and should be used judiciously, particularly in the presence of extensive bruising in the porta hepatis. Furthermore, more recent evidence has shown a considerable mortality (31 per cent) for patients treated by vascular ligation (Flint et al., 1977) and the procedure may be followed by severe deleterious effects, particularly in the presence of concomitant infection. Ligation should not be used in the presence of shattered liver tissue requiring resectional débridement or lobectomy. Immediate control of haemorrhage should not necessarily be bought at the expense of later sepsis and delayed mortality (Atik, 1976).

Wounds accompanied by much devitalization of liver tissue warrant resectional methods in their treatment (Blumgart and Vajrabukka, 1972; Blumgart, 1978). Resectional débridement may be safely employed to remove large amounts of devitalized liver tissue since it exposes the underlying blood and biliary vessels which may be controlled by direct suture ligation. However, for wounds which shatter and disrupt the liver substance deep within its pulp and in which débridement along non-anatomical lines at the periphery of a liver lobe is not possible, formal liver resection is indicated. The need for such resection is almost confined to severe blunt injuries and shotgun wounds and all the cases described in this paper followed severe disruptive blunt injury to the right lobe of the liver.

Mortality and morbidity for blunt liver injury have decreased markedly and the improvement has been in part attributable to more liberal use of resection when necessary. On the other hand, a recent American survey (Walt, 1978) of patients with injury severe enough to warrant resection estimated the mortality of resection to be approximately 50 per cent and argued for a limited use of extensive resection in the emergency situation. Such arguments are valid but should be tempered by the realization that it is difficult to determine the true mortality of liver injury alone. Factors such as speed of transfer to hospital, the number of other organs injured and the experience of the surgical team should be taken into account and mortality figures of 30 per cent or less are now regularly recorded (Little and Williams, 1969; Walt, 1969; Blumgart and Vajrabukka, 1972). In our experience, 3 out of 15 patients (20 per cent) have died following resection for major blunt injury.

The management of hepatic tumours is depressing since untreated patients with hepatocellular carcinoma survive only 3–6 months after diagnosis. Patients with secondary deposits from a primary site in the gastrointestinal tract cannot expect to live 5 years, and the majority will be dead within a year (Foster, 1970; Wood, Gillis et al., 1976; Foster and Berman, 1977; Terblanche, 1977). The results of palliation using radiotherapy and chemotherapy are disappointing. There is some recent evidence that doxorubisin may be helpful in primary hepatobiliary cancer (Johnson et al., 1978), but other studies which have examined these measures together with hepatic dearterialization have suggested that they yield no better results than simple symptomatic relief (Ong and Chan, 1976). Hepatic transplantation for tumour has also been disappointing, and although occasional long term survivors are reported (Calne and Williams, 1977; Putnam and Starzl, 1977) hepatic resection still represents the greatest prospect of cure (Shiu and Fortner, 1975; Ong and Chan, 1976).

Our experience of hepatic resection for primary hepatoma and cholangiocarcinoma is small but nevertheless some important points are worthy of comment. First, of eight primary hepatocellular carcinomas seen in a 5-year period, 3 were in cirrhotic livers and were inoperable. However, 2 of the remaining 5 cases were suitable for resection. Although 1 patient died 18 months after surgery as a result of the development of bone metastases and the other, a girl aged 16, died with recurrent tumour 23 months after initial surgery, excellent palliation was obtained. In both these patients there was involvement of the portal vein and yet resection proved possible by extending the dissection along the course of the right branch of the portal vein within the liver substance while preserving the posterosuperior and anteroinferior branches of vessels and ducts. This allows an extension of the limits of operability for tumour close to the hilus of the liver. There is no indication for resection if there is evidence of extrahepatic involvement or if there are several malignant foci in the liver. On the other hand, hilar involvement with spread of the tumour across anatomical boundaries is no bar to resection. McBride and Wallace (1972) and Miller (1974) have described multiple segmental resections of the liver for hepatic growths and although Starzl et al. (1975) doubt whether there is a necessity for such an operation, we believe, as do Ong and Chan (1976), that such dissection is occasionally necessary and can give good results.

The risk of operation and chance of success must be weighed against the expectations of complete hepatic resection and liver transplantation. However, transplantation is hazardous and the patient requires postoperative immunosuppression.

The timing of resection for secondary tumour is important, and because of the risks of infection, it should only rarely be performed at the same time as colonic resection. On the other hand, we believe that there is no reason to wait for prolonged periods before proceeding to hepatic resection, nor do we believe that there is any particular advantage in selecting for resection only those cases who develop secondary growths some years after removal of the primary. In experienced hands the mortality of resection for metastatic lesions is small (Ong and Lee, 1975) and a 5-year survival of between 15 and 40 per cent is to be expected (Wilson and Adson, 1976; Foster and Berman, 1977).

The relief of biliary obstruction by means of hepatic resection has not been widely practised but there are two main indications. First, hepatic resection can be valuable in patients with primary tumours at the confluence of the bile ducts. Inoperable cholangiocarcinoma in this area can be managed by means of intubation as described by Terblanche and Louw (1973). However, for potentially resectable lesions a more aggressive surgical approach seems warranted. Precise preoperative evaluation, including PTC, ERCP, arteriography and splenoportography, will define most clearly inoperable lesions and leave a few selected cases for attempted resection. The technique we describe in which an initial hepatotomy is carried out and the tumour assessed either for local excision or for excision together with hepatic lobectomy has allowed us to proceed to a resection so extensive as to necessitate three separate hepaticojejunostomy anastomoses to a single loop of jejunum within second order ducts in the right lobe of the liver (Blumgart, 1978). Such initial hepatotomy does not preclude palliative intubation should the lesion prove inoperable.

Secondly, hepatic resection can be employed in certain patients with benign biliary strictures. It is true that the majority of iatrogenic bile duct injuries can be dealt with by an infrahepatic reconstruction or by use of the 'mucosal graft' technique (Smith, 1972). The long term results of the latter procedure remain to be fully assessed and the method is inapplicable in the presence of small intrahepatic ducts. We have preferred splitting the liver by means of hepatotomy in a similar manner to that described above (Benjamin and Blumgart, 1978), so allowing mucosa-to-mucosa suture. In 2 of our cases hepatic resection was performed to allow access for the construction of an intrahepaticojejunostomy. Modest resection of the quadrate lobe of the liver overlying the hepatic hilus has also been performed in a number of cases and has allowed precise mucosa-to-mucosa suture. All the 6 patients in whom we carried out resection and anastomosis for benign bile duct stricture are alive and well at periods varying from 9 months to 5 years. In addition, 3 other patients not included in the series had hepatotomy (liver split) without hepatic resections. Of these, 2 are alive and well 18 months and 1 month respectively after operation, the other died in the postoperative period with bacteraemia and multiple organ failure.

Hepatic resection is well tolerated and regeneration of the liver is rapid (Blumgart et al., 1971). When performed for severe injury to the liver the procedure is life-saving and the long-term results excellent. Similarly, resection of the liver substance to allow access for reconstruction by means of biliary enteric anastomosis in selected cases gives good results. Hepatic resection for tumour offers, at best, the prospect of cure and at the very least significant prolongation of life with excellent palliation in a significant number of patients. The operative and intra-hospital mortality is acceptable.

References

AARON S., FULTON R. L. and MAYS E. T. (1975) Selective ligation of the hepatic artery for trauma of the liver. *Surg. Gynecol. Obstet.* **141**, 187–189.

ADSON M. A. and BEART R. W. (1977) Elective hepatic resections. *Surg. Clin. North Am.* **57**, 339–360.

ALLISON M. E. M., MOSS N. G., FRASER M. M. et al. (1978) Renal function in chronic obstructive jaundice: a micropuncture study in rats. *Clin. Sci. Mol. Med.* **54**, 649–659.

ATIK M. (1976) Operative cholangiography and special technical consideration in the management of severe injury of the liver. *Surg. Gynecol. Obstet.* **143**, 741–748.

BALASEGARAM M. (1970) Hepatic surgery: present and future. *Ann. R. Coll. Surg. Engl.* **47**, 139–158.

BENJAMIN I. S., ALLISON M. E. M., MOULE B. et al. (1973) The early use of fine needle percutaneous transhepatic cholangiography in an approach to the diagnosis of jaundice in a surgical unit. *Br. J. Surg.* **65**, 92–98.

BENJAMIN I. S. and BLUMGART L. H. (1979) Biliary bypass and reconstructive surgery. In: *Liver and Biliary Disease: a Pathophysiological Approach.* Philadelphia, Saunders.

BLUMGART L. H. (1978) Biliary tract obstruction. New approaches to old problems. *Am. J. Surg.* **135**, 19–31.

BLUMGART L. H., LEACH K. G. and KARRAN S. J. (1971) Observations on liver regeneration after right hepatic lobectomy. *Gut* **12**, 922–928.

BLUMGART L. H. and VAJRABUKKA T. (1972) Injuries to the liver; analysis of 20 cases. *Br. Med. J.* **1**, 158–164.

BOLTON P. M., WOOD C. B., QUARTEY-PAPAFIO J. B. et al. (1973) Blunt abdominal injury: a review of 59 consecutive cases undergoing surgery. *Br. J. Surg.* **60**, 657–663.

CALNE R. Y., MCMASTER P. and PENTLOW B. D. (1979) The treatment of major liver trauma by packing with transfer of the patient for definitive treatment. *Br. J. Surg.* **66**, 338–339.

CALNE R. Y. and WILLIAMS R. (1977) Orthoptic liver transplantation—the first 60 patients. *Br. Med. J.* **1**, 471–476.

DAWSON J. L. (1965) Postoperative renal function in obstructive jaundice: effect of a mannitol diuresis. *Br. Med. J.* **1**, 82–86.

FLEMMA R. J., FLINT L. M., OSTERHOUT S. et al. (1967) Bacteriologic studies of biliary tract infection. *Ann. Surg.* **166**, 563–572.

FLINT L. M., MAYS E. T., AARON W. S. et al. (1977) Selectivity in the management of hepatic trauma. *Ann. Surg.* **185**, 613–618.

FOSTER J. H. (1970) Survival after liver resection for cancer. *Cancer* **26**, 493–502.

FOSTER J. H. and BERMAN M. M. (1977) Solid liver tumours. In: P. EBERT (ed.) *Major Problems in Clinical Surgery*, 22. Philadelphia, Saunders.

GOLDSMITH N. A. and WOODBURNE R. T. (1957) The surgical anatomy pertaining to liver resection. *Surg. Gynecol. Obstet.* **105**, 310–318.

HEALEY J. E. (1954) Clinical anatomic aspects of radical hepatic surgery. *J. Int. Coll. Surg.* **22**, 542–544.

JOHNSON P. J., WILLIAMS R., THOMAS H. et al. (1978) Induction of remission in hepatocellular carcinoma with doxorubicin. *Lancet* **1**, 1006–1009.

KEIGHLEY M. R. B. (1977) Micro-organisms in the bile. *Ann. R. Coll. Surg. Engl.* **59**, 328–334.

LITTLE J. M. and WILLIAMS C. W. (1969) Improved mortality in the management of liver injuries. *Br. J. Surg.* **56**, 603–610.

LONGMIRE W. P., TROUT H. H., GREENFIELD J. et al. (1974) Elective hepatic surgery. *Ann. Surg.* **179**, 712–721.

MCBRIDE C. M. and WALLACE S. (1972) Cancer of the right lobe of the liver. *Arch. Surg.* **105**, 289–296.

MCINDOE A. H. and COUNSELLOR V. S. (1927) The bilaterality of the liver. *Arch. Surg.* **15**, 589–594.

MILLER D. R. (1972) Median sternotomy extension of abdominal incision for hepatic lobectomy. *Ann. Surg.* **175**, 193–196.

MILLER T. R. (1974) Neoplasms of the liver. In: R. MAINGOT (ed.) *Abdominal Operations*, vol. 11. New York, Appleton-Century-Crofts, pp. 1226–1246.

ONG G. B. (1977) Techniques and therapies for primary and metastatic liver cancer. In: *Current Problems in Cancer*, vol. 2. Chicago, Year Book.

ONG G. B. and CHAN P. K. W. (1976) Primary carcinoma of the liver. *Surg. Gynecol. Obstet.* **143**, 31–38.

ONG G. B. and LEE N. W. (1975) Hepatic resection. *Br. J. Surg.* **62**, 421–430.

PUTNAM C. W. and STARZL T. E. (1977) Liver transplantation. *Surg. Clin. North Am.* **57**, 361–373.

SHINGLETON W. W. (1977) In: Discussion of Flint et al. (q.v.).

SHIU M. H. and FORTNER J. G. (1975) Current management of hepatic tumours. *Surg. Gynecol. Obstet.* **140**, 781–788.

SMITH R. (1972) Strictures of the bile ducts. In: BADENOCH J. and BROOKE B. (ed.) *Recent Advances in Gastroenterology*, 2nd ed. Edinburgh, Churchill Livingstone, pp. 331–341.

STARZL T. E., BELL R. H., BEART R. W. et al. (1975) Hepatic trisegmentectomy and other liver resections. *Surg. Gynecol. Obstet.* **141**, 429–437.

TORM F. K. and LONGMIRE W. P. (1971) A simplified clamp for hepatic resection. *Surg. Gynecol. Obstet.* **133**, 103–104.

TEMPLETON J. Y. and DODD G. D. (1963) Anatomical separation of the right and left lobes of the liver for intrahepatic anastomosis of the biliary ducts. *Ann. Surg.* **57**, 287–291.

TERBLANCHE J. (1977) Liver tumours. *Br. J. Hosp. Med.* **17**, 103–114.

TERBLANCHE J. and LOUW J. H. (1973) 'U' tube drainage in the palliative therapy of carcinoma of the main hepatic duct system. *Surg. Clin. North Am.* **53**, 1245–1255.

VAJRABUKKA T., BLOOM A. L., SUSSMAN M. et al. (1975) Postoperative problems and management after hepatic resection for blunt injury to the liver. *Br. J. Surg.* **62**, 189–200.

WADDELL W. R. (1967) Exposure of intrahepatic ducts through interlobar fissure. *Surg. Gynecol. Obstet.* **124**, 491–500.

WALT A. J. (1969) The surgical management of hepatic trauma and its complications. *Ann. R. Coll. Surg. Engl.* **45**, 319–339.

WALT A. J. (1978) The mythology of hepatic trauma—or Babel revisited. *Am. J. Surg.* **135**, 12–18.

WILSON S. M. and ADSON M. A. (1976) Surgical treatment of hepatic metastases from colorectal cancers. *Arch. Surg.* **3**, 330–334.

WOOD C. B., CAPPERAULD I. and BLUMGART L. H. (1976) Bioplast fibrin buttons for the control of haemorrhage of the liver following biopsy and partial resection. *Ann. R. Coll. Surg. Engl.* **58**, 401–404.

WOOD C. B., GILLIS C. R. and BLUMGART L. H. (1976) A retrospective study of the natural history of patients with liver metastases from colorectal cancer. *Clin. Oncol.* **2**, 285–288.

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In vitro dissolution of human gallstones: the efficacy of heparinized solutions

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SUMMARY

The use of heparinized solutions to dissolve or fragment stones retained in the biliary tree after surgery is still controversial. In this in vitro study heparin in concentrations of up to 100 000 u/l did not dissolve or fragment the stones examined, nor did it enhance the dissolution properties of the bile salt, sodium cholate.

THE treatment of stones retained in the biliary tree following surgery with solutions introduced via the T tube is well established. Different claims of success have been made for a variety of solutions, the most consistently effective in dissolving gallstones being bile salt solutions (Toouli et al., 1975).

The role of heparin in the treatment of stones retained in the biliary tree is controversial. Clinical studies have shown a high rate of success in eliminating stones from the biliary tree (Gardner, 1973). However, *in vitro* studies have cast doubt on the claims that heparin acts by dissolving or fragmenting the gallstones (Hardie et al., 1977).

In this report we describe the findings of an *in vitro* study of the effect of heparin in dissolving cholesterol gallstones. In addition, the combined effect of sodium cholate and heparin solutions was compared with that of sodium cholate solutions alone.

Materials and methods

Gallstones

Human cholesterol gallstones were obtained from the gallbladder of one patient having cholecystectomy. The stones were rinsed with normal saline and six representative stones were analysed for their cholesterol content. These stones were composed of 95 ± 5 per cent cholesterol. The stones were multifaceted and of variable size and weight. Stone weight was used as the parameter that determined changes in the stone brought about by immersion in the test solutions.

Solutions

The composition of the various solutions tested is shown in *Table I*. The solutions were prepared as follows:

1. Sodium cholate (200 mM) (Weddel Pharmaceuticals). The bile salt was dissolved in sodium chloride (150 mM).
2. Heparin (Weddel Pharmaceuticals). Sodium heparin was added to sodium chloride (150 mM) at a concentration of 100 000 u/l. The heparin contained 0·15 per cent chlorocresol as a preservative.
3. Sodium cholate (200 mM) plus heparin. Sodium heparin was added to sodium cholate (200 mM) solutions at concentrations of 25 000, 50 000 and 100 000 u/l of solution.

Table I: TEST SOLUTIONS

Sodium chloride 150 mM
Sodium cholate 200 mM
Sodium cholate 200 mM plus heparin 25×10^3 u/l
Sodium cholate 200 mM plus heparin 50×10^3 u/l
Sodium cholate 200 mM plus heparin 100×10^3 u/l
Sodium chloride 150 mM plus heparin 100×10^3 u/l

Dissolution experiments

Twenty millilitres of each solution were placed in 50-ml flasks and a single human cholesterol gallstone of known weight was placed in each flask. The flasks were placed in a constant temperature water bath at 37 ± 1 °C and gently agitated.

On days 4, 8, 12 and 16 the stones were removed from the flasks, rinsed with sodium chloride and left to dry at room temperature for an hour on filter paper. The solutions were renewed, the stones weighed and then replaced in the flasks. To overcome the possibility of bacterial degradation of the heparin solutions, sodium heparin was added to the flasks on days 2, 6, 10 and 14 in quantities identical to the initial concentrations. Therefore, between these days and the days when the solutions were renewed, the total concentration of heparin in each flask was doubled.

Estimation of rate of dissolution

Four stones were used in each group. The stones were selected so that the weight range in each group was similar. In order to facilitate comparison, the stone weights on each test day were expressed as a percentage of the original weight. The means of the percentage changes in weight for each test day were determined.

Using Student's *t* test, the results were compared for each solution tested. The statistical analysis was carried out on the weights of the individual stones on the test days and the means of the percentage changes in weight.

Results (Table II)

Effect of normal saline

Four stones were immersed in normal saline solution for 16 days. There was no significant change in the weight of the stones.

Effect of addition of heparin

Four stones were immersed in heparinized saline solution (concentration = 100 000 u/l). There was no significant change in the weight of the stones during 16 days of continuous immersion. In addition, there was no visible fragmentation of the stones.

Effect of sodium cholate solution

Four stones were immersed in 200 mM sodium cholate solution. There was a significant ($P < 0{\cdot}05$) decrease in the weight of all the stones, indicating dissolution. The stones were reduced to less than 50 per cent of their initial weight after 16 days of continuous immersion.

Effect of addition of heparin

Heparin was added to 200 mM sodium cholate solutions to form three groups of solutions at concentrations of 25 000 u/l, 50 000 u/l and 100 000 u/l respectively. In each group of solutions there were four flasks and a stone was added to each flask. There was a significant ($P < 0{\cdot}05$) decrease in the weight of all the stones, and this decrease in weight was progressive over 16 days. There was no significant difference in the weight loss achieved by the solutions containing different concentrations of heparin, and there was no significant difference in the weight loss achieved by solutions of sodium cholate alone and sodium cholate plus heparin. Therefore, heparin did not enhance the dissolving capacity of sodium cholate

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Table II: DISSOLUTION OF GALLSTONES BY COMBINATIONS OF SALINE, HEPARIN AND SODIUM CHOLATE

Solution	No. of stones	Initial weight of stones (mg)	% of original weight on day 4	8	12	16
Sodium chloride	4	333 (287–382)	99 (99–99)	104 (104–105)	103 (102–104)	102 (101–104)
SC 200 mM	4	326 (225–414)	83 (78–87)	74 (67–78)	57 (45–65)	42 (27–52)
SC 200 mM+heparin 25 × 10^3 u/l	4	330 (243–410)	83 (79–86)	74 (69–78)	57 (48–65)	43 (30–52)
SC 200 mM+heparin 50 × 10^3 u/l	4	278 (251–400)	84 (80–87)	75 (70–78)	58 (52–63)	44 (36–51)
SC 200 mM+heparin 100 × 10^3 u/l	4	328 (258–390)	84 (81–86)	74 (71–78)	59 (55–64)	44 (43–45)
Sodium chloride+heparin 100 × 10^3 u/l	4	328 (270–385)	99 (98–100)	105 (103–107)	103 (102–106)	103 (100–105)

Values are mean and range.
SC, Sodium cholate.

solutions. In addition, there was no evidence of fragmentation in any of the stones.

Discussion

The aim of this study was to investigate under controlled laboratory conditions the claims that heparin is effective in dissolving human cholesterol gallstones.

Our results show that heparin alone does not cause dissolution or fragmentation of human cholesterol gallstones. In addition, they show that heparin does not accelerate or enhance the dissolving capacity of sodium cholate (200 mM) solutions at the concentrations tested.

There is still much dispute as to the effectiveness of heparin in dissolving cholesterol gallstones. Gardner (1973) has reported success in treating, with heparin, stones retained in the common bile duct, and Lahana et al. (1974) have shown fragmentation of stones suspended in heparinized solutions *in vitro*. However, Hardie et al. (1977) and McCombs et al. (1973) have reported no effect of this substance on gallstone fragmentation or dissolution. The present study supports the findings of the latter authors. One of the reasons for the discrepancies in the results from different centres may be variation in methodology. In some studies the stones were allowed to float freely (Toouli et al., 1975), in others they were retained in a basket or bag (Hardie et al., 1977) and in others the solution was actively stirred mechanically (Lahana et al., 1974). Methods that actively disturb the suspending solution may traumatize the stones and therefore promote fragmentation.

We have overcome these problems in the present study by simplifying the design. The stones were immersed free in solution without the added mechanical trauma of a stirrer within the flasks. Potential criticisms of saturation or degradation of the dissolution agent were overcome by renewing the solutions every 4 days and by the addition of extra heparin after alternate 48-h periods. The action of heparin in producing fragmentation of gallstones is controversial. Ostrewitz and Gardner (1970) have proposed a theoretical argument for the action of heparin, based on adsorption of the highly charged heparin polymer to the outer surface of small stone fragments with consequent repulsion of adjacent particles due to their similar negative charge. While this explains the action of heparin in stabilizing small particles in colloidal solutions, it does little to explain the fragmentation of individual large gallstones, which has been reported by these workers.

Furnival et al. (1977) observed an increased rate of gallstone dissolution and fragmentation when heparin was added to sodium cholate solutions. This has not been confirmed in the present study. The theoretical mechanism proposed by these workers, involving increased repulsion of bile salt micelles, assumes that the highly negatively charged heparin polymer can be incorporated into the negatively charged micelles. That adsorption of two aggregates of similar charge is possible under these circumstances has not been proved. The assumption that increased separation of bile salt micelles is associated with increased cholesterol solubilization is also unproved.

On the basis of the present study, the use of heparin alone, or to augment the available bile salt preparations, in dissolving stones retained in the biliary tree cannot be recommended.

References

FURNIVAL C. M., BURNETT W., GREEN K. et al. (1977) *In vitro* studies of gallstone dissolution. The effect of added heparin in bile salt solutions. *Aust. NZ J. Surg.* **47**, 828–831.

GARDNER B. (1973) Experience with the use of intracholedochal heparinized saline for the treatment of retained common duct stones. *Ann. Surg.* **177**, 240–244.

HARDIE I. R., GREEN M. K., BURNETT W. et al. (1977) *In vitro* studies of gallstone dissolution using bile salt solutions and heparinized saline. *Br. J. Surg.* **64**, 572–576.

LAHANA D. A., BONORRIS C. G. and SCHOENFIELD L. J. (1974) Gallstone dissolution *in vitro* by bile acids, heparin and quaternary amines. *Surg. Gynecol. Obstet.* **138**, 683–685.

MCCOMBS P. R., QUARANTILLO E. P. JUN. and SELTZER M. H. (1973) Heparin treatment of common duct stones. *N. Engl. J. Med.* **289**, 106.

OSTREWITZ A. and GARDNER B. (1970) Studies of bile as a suspending medium and its relationship to gallstone formation. *Surgery* **68**, 329–333.

TOOULI J., JABLONSKI P. and WATTS J. MCK. (1975) Dissolution of human gallstones. The efficacy of bile salts, bile salt plus lecithin and heparin solutions. *J. Surg. Res.* **19**, 43–53.

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Intestinal bacterial metabolism of protein and bile acids: role in pathogenesis of hepatic disease after jejuno-ileal bypass surgery

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SUMMARY

Jejunal bacterial colonization and intestinal metabolism of bile acids and protein by bacteria have been investigated in 12 patients with abnormal liver histology following jeujno-ileal bypass surgery for obesity.

Aerobic and/or anaerobic colonic flora was present in jejunal aspirates from 8 of 12 bypass patients, but in none of the controls. Intestinal protein metabolism and bile acid deconjugation (measured by urinary indican excretion and ^{14}C-glycocholic acid breath test) was significantly enhanced in bypass patients.

Intestinal bacterial overgrowth, with abnormal intestinal metabolism by bacteria of ingested nutrients and bile acids, could contribute to hepatic disease after bypass surgery via the production of endogenous hepatotoxins.

JEJUNO-ILEAL bypass is a highly effective treatment for selected patients with gross refractory obesity, but this operation may be followed by a variety of complications. In addition to anticipated nutritional disturbances, there are a number of unexplained sequelae including arthralgia, colonic pseudo-obstruction and liver disease. In most cases the hepatic disturbance, characterized by hepatic steatosis and patchy hepatocellular necrosis, is subclinical. However, death from hepatic failure has been reported in between 2 and 8 per cent of patients (Maxwell et al., 1977). While bacteria have been implicated in the arthralgia and colonic pseudo-obstruction following bypass surgery (Wands et al., 1976; Barry et al., 1977), the pathogenesis of liver disease, the most serious complication of this operation, remainds unexplained.

In previous studies neither hepatitis B infection nor halothane anaesthesia could be implicated (Maxwell et al., 1977). Although nutritional disturbances may contribute, there is no simple relationship between altered liver function and weight loss following bypass (Salmon and Reedyk, 1975). As abnormal intestinal bacterial metabolism of ingested nutrients and bile acids might be relevant to post-bypass hepatic dysfunction, we studied the effects of jejuno-ileal bypass on the bacterial flora in the jejunum proximal to the excluded segment, and on the bacterial metabolism of tryptophan and bile acids within the intestine.

Patients and methods

Twelve unselected patients (all female, aged 28–64 years) were investigated at least 3 years after jejuno-ileal bypass surgery as part of a routine postoperative evaluation. The operation performed was a modification of the standard procedure. Four inches (10 cm) of jejunum measured from the duodenojejunal junction were anastomosed end to side to the terminal 10 in (25 cm) of ileum, thus producing an isoperistaltic excluded segment of jejuno-ileum several feet in length. None of the bypass patients had any clinical or biochemical features of liver disease at the time of study. However, liver biopsy revealed extensive fatty change, together with variable degrees of patchy focal necrosis, portal tract hypercellularity and parenchymal fibrosis, in all patients.

Five control subjects, matched for age and sex, were selected from obese patients awaiting jejuno-ileal bypass surgery and from hospital inpatients. None of the controls had undergone bowel surgery, nor had any of the patients or controls recently received any antibiotic therapy. The nature of the study was explained, and all subjects gave informed consent before investigation.

The following investigations were performed:

Jejunal aspiration: A jejunal aspirate was obtained from the fasting subject by passing a sterile Andersen radio-opaque long weighted sump tube transnasally and positioning it, under radiological control, just distal to the duodenojejunal flexure. Two millilitres of jejunal contents were aspirated into a sterile syringe, any air was excluded and the syringe was made airtight with a cap. Samples were transported to the laboratory where they were either cultured immediately or frozen for culture at a later date. Aliquots (1 ml) of samples to be frozen were injected into a carbon dioxide gassed vial containing 9 ml of 10 per cent glycerol broth. The vial was then immersed in a methanol/acetone/solid CO_2 mixture in a vacuum flask. Frozen samples were stored at −20 °C and cultured within 3 weeks.

Aerobic/anaerobic bacterial culture: Serial logarithmic dilutions of the aspirate were made in brain–heart infusion broth up to 10^{-8}. Equal volumes of each dilution (0·1 ml) were spread on to a series of selective and non-selective media and incubated under appropriate atmospheric conditions for up to 5 days. Bacterial counts and identifications of species were carried out according to standard methods as described by Holderman and Moore (1972) and Cowan and Steel (1974).

Bile acids in postprandial bile: After obtaining the initial fasting jejunal aspirate for bacterial culture, the patient was given a standard Lundh test meal to stimulate bile secretion. Bile was siphoned off for 2 h into a sterile bottle kept on ice. Samples were stored at −20 °C before analysis for deconjugated bile acids by thin-layer chromatography. This was carried out on 0·25 mm silica gel plates developed with solvent systems using trimethylpentane : ethylacetate : acetic acid (5 : 5 : 1) and benzene : isopropanol : acetic acid (30 : 10 : 1) (Eneroth, 1963).

Bile acid breath test: Hourly breath samples were collected into hyamine hydroxide for 8 h after oral administration of 5 μCi ^{14}C-glycocholate with a Lundh test meal after an overnight fast. No jejunal fluid was aspirated on this occasion. ^{14}C radioactivity was measured by liquid scintillation counter and expressed as a percentage of the dose given per mmol $CO_2 \times$ body weight (kilogrammes) (James et al., 1973).

Urinary indican excretion: Urine was collected for 24 h into bottles containing thymol as preservative. All subjects were on a normal diet, taking 60–100 g protein daily. The indican content was measured by the spectrophotometric method of Curzon and Walsh (1962). Urinary creatinine excretion was also measured to evaluate the completeness of urine collection.

Results

Bacterial culture

Counts of aerobic organisms in the group of 12 post-bypass patients were higher than in the group of 5

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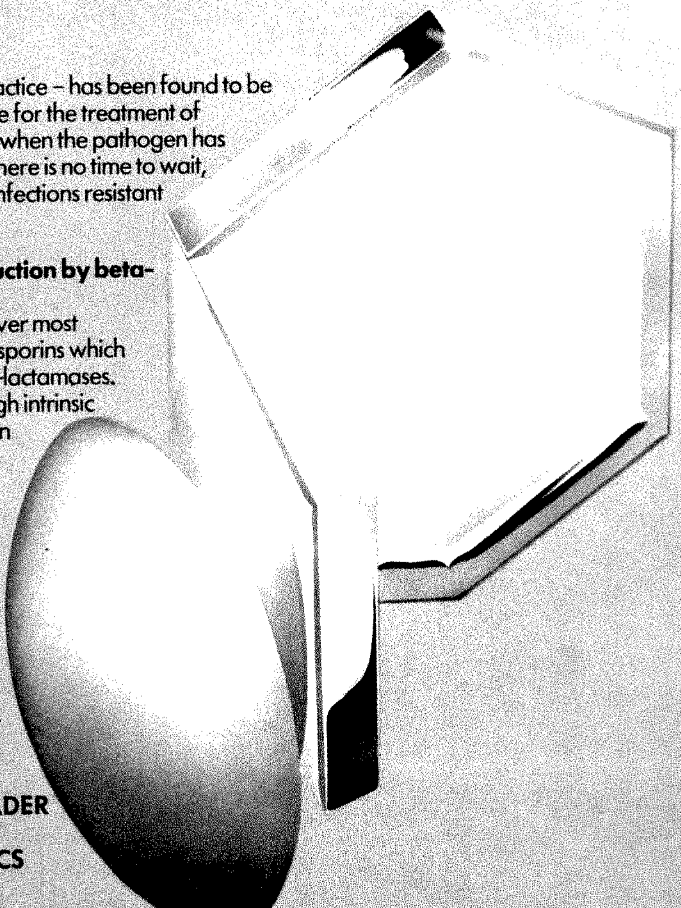

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Infants and Children: 30 to 100mg/kg/day in three or four divided doses. 60mg/kg/day will be appropriate for most infections.
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Contra-indications
Hypersensitivity to cephalosporins.
Precautions
Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins.
As with all drugs, Zinacef should be administered with caution during the early months of pregnancy.
Zinacef does not interfere with enzyme-based tests for glycosuria. Cephalosporins interfere with tests for glycosuria which use copper reduction or ferricyanide methods and with the alkaline picrate assay for creatinine. As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms.
Zinacef should not be mixed in the syringe with aminoglycoside antibiotics.
Reduce dosage when renal function is markedly impaired.
Cephalosporins at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as frusemide, as these combinations are suspected of adversely affecting renal function. Clinical experience with Zinacef has shown that this is not likely to be a problem at the recommended dose levels.
Side effects
Adverse reactions are rare and generally mild and transient, e.g., rashes, gastro-intestinal disturbance, candida intertrigo, decreased haemoglobin concentration, eosinophilia, a positive Coombs' test, transient rises in serum liver enzymes and transient pain (after i.m. injection).
Storage
Protect from light.
Product Licence number: 4/0253
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5 x 250mg	£0·70 per vial
5 x 750mg	£2·10 per vial
1·5 grams	£4·20

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Full prescribing information on Zinacef (trade mark) is available from:
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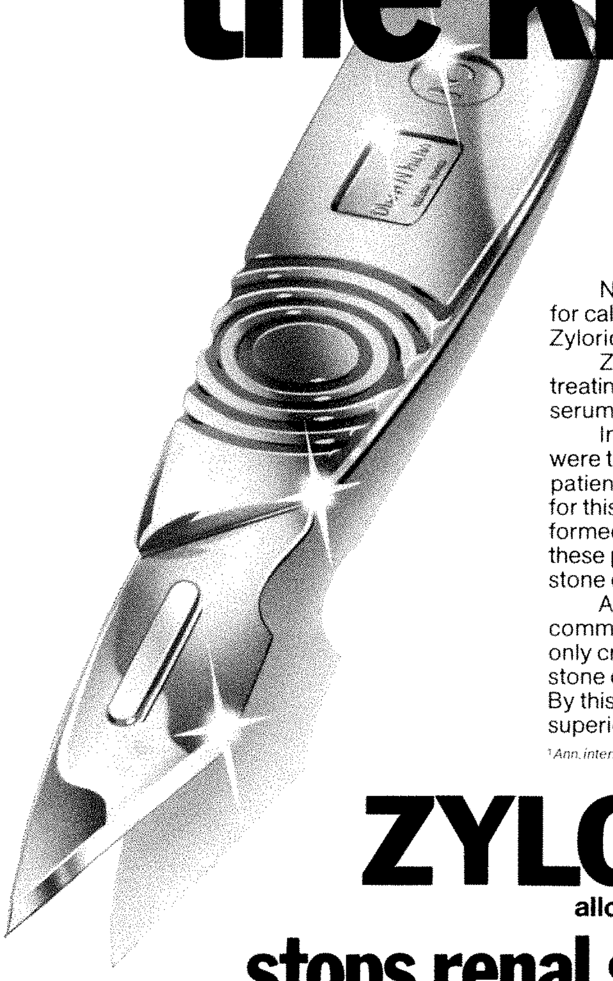

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Now there is a practical alternative to surgery for calcium renal lithiasis: long-term prophylaxis with Zyloric.

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A leading article[2] in the *British Medical Journal*, commenting on another clinical paper[3] stated "...the only criterion of success in the treatment of calcium stone disease is total cessation of stone formation. By this criterion, allopurinol (Zyloric) was greatly superior to the placebo."

[1] *Ann. intern. Med.* (1977), **87**, 404. [2] *Brit. med J.* (1977), **2**, 1302. [3] *J. Urol.* (1977) **117**, 690.

ZYLORIC-300

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stops renal stones starting

Indications: Conditions of excess body urate including gouty arthritis. Prophylaxis of calcium renal lithiasis in patients with raised serum or urinary uric acid.
Dosage: The average adult dose is one Zyloric-300 tablet daily, plus an anti-inflammatory agent or colchicine for at least one month. Dosage should be adjusted by monitoring serum uric acid until the required level is attained. It has rarely been found necessary to exceed 900 mg per day. Children: 10-20 mg/kg bodyweight/day.
Contra-indications: None, other than known intolerance to Zyloric. **Precautions:** If Puri-Nethol* (6-mercaptopurine) or Imuran* (azathioprine) is given concurrently with Zyloric, the dose of Puri-Nethol or Imuran should be reduced to one quarter of the usual dose. Caution should be observed in pregnancy. Zyloric is not a treatment for acute gout, but prophylactic treatment with Zyloric may be started at the same time as anti-inflammatory treatment. **Side-effects:** These are usually rare and mostly of a minor nature. They include skin reactions, generalised hypersensitivity, gastro-intestinal disorders, blood and lymphatic disorders. **Presentation:** Zyloric-300* is available as 300 mg scored, creamy-white tablets in packs of 28. Basic NHS cost: £5.96 per pack. PL 3/0092. Also available: 100 mg tablets in bottles of 100. Additional information about Zyloric* (allopurinol) is available on request.

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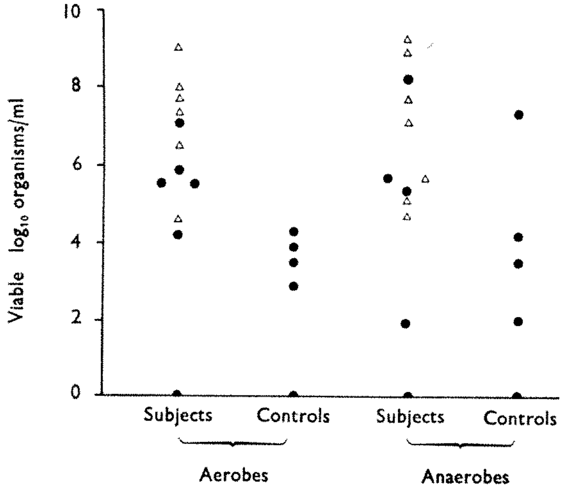

Fig. 1. Log counts of aerobic and anaerobic organisms from proximal jejunal aspirates in post-bypass patients and controls. ●, Small intestinal flora. △, Colonic flora.

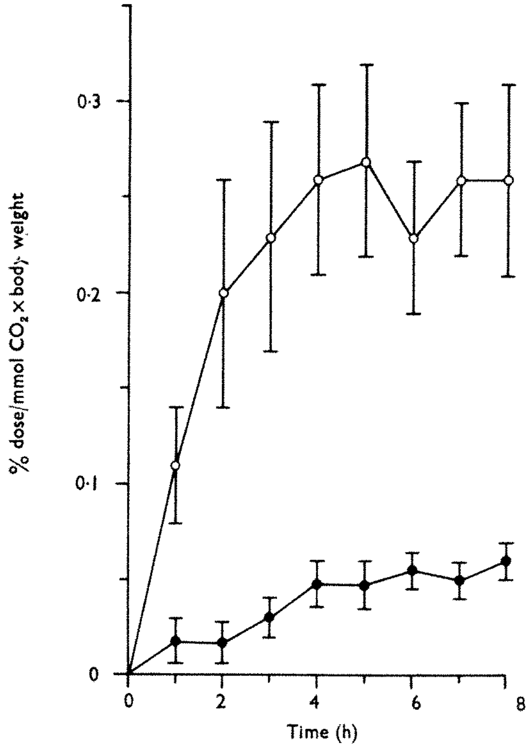

Fig. 2. Bile acid breath test in post-bypass patients (○) and controls (●). All results given as mean ± s.e. mean.

control subjects ($P<0·02$, Mann–Whitney U test). Counts of anaerobic organisms in the two groups were not significantly different ($P>0·05$, Mann–Whitney U test) (*Fig.* 1).

A separate estimation was made regarding the presence or absence of colonic flora in jejunal aspirates. Aerobic colonic flora were present in 6 of the post-bypass patients but in none of the controls ($P=0·075$, Fisher's exact test). Anaerobic colonic flora were present in 7 of the post-bypass patients but in none of the controls ($P=0·04$, Fisher's exact test). Aerobic and/or anaerobic colonic flora was present in 8 of the post-bypass patients but in none of the controls ($P=0·02$, Fisher's exact test).

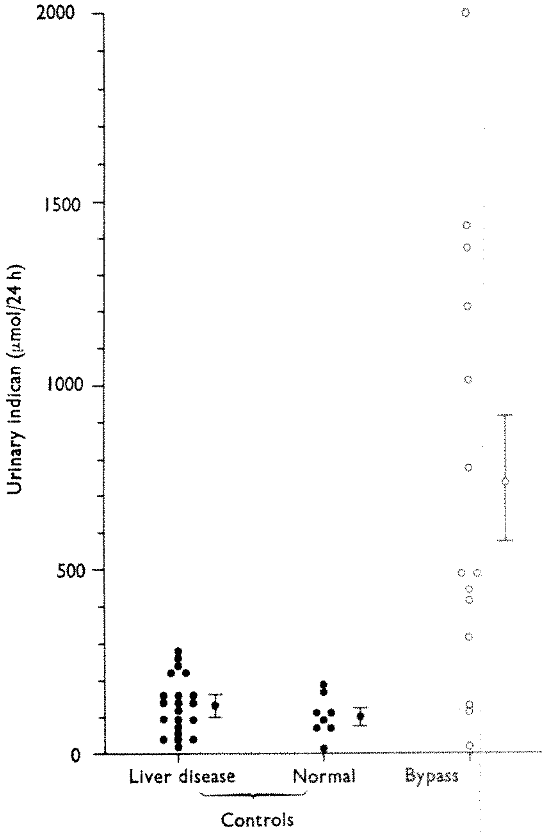

Fig. 3. Urinary indican excretion (μmol/24 h) in post-bypass patients (○), normal controls and liver disease controls (●). All results given as mean ± s.e. mean.

Neither subjects nor controls had aerobic bacteria which could deconjugate bile salts. Ten out of 12 subjects and 4 out of five controls had anaerobic bacteria which could deconjugate bile salts. In the control group only one species was present which could deconjugate bile salts, i.e. veillonella. However, in the group of subjects, a variety of deconjugating bacteria was present. These included bacteroides, veillonellae, bifidobacteria and other anaerobic Gram-positive rods. More than one species was often present in each of the subjects.

Thin-layer chromatography

Thin-layer chromatography using two different solvent systems showed the presence of deconjugated bile acid in jejunal aspirate from 2 of the 12 post-bypass patients. One patient showed the presence of deconjugated deoxycholic acid and the other showed deconjugated cholic acid, chenodeoxycholic acid and deoxycholic acid.

Bile acid breath test

There was increased deconjugation of bile acids in the group of 11 post-bypass patients compared with the group of 11 normal control subjects ($P<0{\cdot}001$, Student's *t* test) (*Fig.* 2).

Urinary indican excretion

Urinary indican excretion was higher in the group of 15 post-bypass patients compared with the group of 21 liver disease control patients ($P<0{\cdot}001$, Student's *t* test) and with the group of 15 normal control subjects ($P<0{\cdot}01$, Student's *t* test) (*Fig.* 3).

Discussion

These studies have clearly demonstrated bacterial overgrowth in the proximal jejunum in the majority of patients after jejuno-ileal bypass. Elevated counts of aerobes and/or anaerobes were found in 10 of 12 subjects and in 8 of these the flora was colonic in type.

These results are in keeping with previous reports that bacterial colonization of the small bowel occurs following bypass (Dano et al., 1974; Barry et al., 1977), but the mode of colonization is uncertain. The bacterial overgrowth with a flora that is often colonic in type may be related to the proximity of the jejunum to the ileocaecal valve, and is similar to that found following massive small intestinal resection (Kristensen et al., 1974). Alternatively, the proximity of the surgically produced anatomical blind loop may contribute to bacterial colonization in the proximal jejunum. Although isoperistaltically emptying segments are not generally considered to function as blind loops (Donaldson, 1965), the extreme lengths of the bypassed loop may invalidate this assumption (Brown et al., 1974).

The presence of an abnormal jejunal flora in the majority of patients was accompanied by evidence of abnormal intestinal metabolism of bile salts and protein in all subjects studied after bypass. It is of interest that many of the bacterial species identified from jejunal aspirates in these subjects are known to be capable of deconjugating bile salts (Drasar and Hill, 1974). From the present studies we are unable to distinguish the relative contribution of the residual small intestine left in circuit, the bypassed segment or the colon to the intestinal metabolism we have demonstrated. However, as deconjugated bile acids were present in jejunal aspirate from only a minority of patients studied, it is likely that intestinal bacterial metabolism of bile salts and nutrients takes place largely at more distal sites.

Although intestinal bacteria have been implicated in the arthralgia and colonic pseudo-obstruction that may occasionally complicate intestinal bypass, their role in the development of post-bypass hepatic dysfunction is less well established. Experimental animal studies investigating the effect of antibacterial drugs on the development of hepatic changes after intestinal bypass have produced conflicting results (McClelland et al., 1970; Hollenbeck et al., 1975). However, it is of interest that in both the dog and the rat, liver function appears to be more disturbed after bypass than after comparable resection (Hollenbeck et al., 1975; Rutter et al., 1978).

The pathogenesis of liver dysfunction after intestinal bypass is almost certainly multifactorial. Nevertheless, our clinical studies provide some indirect evidence for the involvement of bacteria. Intestinal bacterial metabolism of proteins and amino acids, which we have demonstrated indirectly from elevated urinary indican excretion, may contribute to the hypoproteinaemia and deficiencies in circulating amino-acids which have been observed after bypass (Moxley et al., 1974). Moreover, protein deficiency enhances the hepatotoxic effect of bile acids (Carey et al., 1966) and alcohol (Lieber, 1974).

The striking intestinal deconjugation of bile acids that we have demonstrated could provide an explanation for the earlier observation that grossly elevated serum levels of deconjugated bile acids, including lithocholic acid, a known hepatotoxin, occur after bypass (Sherr et al., 1974). Furthermore, there is evidence that small quantities of alcohol are produced by these patients (Mezey et al., 1975), presumably by intestinal bacterial fermentation of ingested carbohydrate. This finding may be relevant to the close histological similarity between the hepatic changes occurring after jejuno-ileal bypass and those found in alcoholic liver disease (Peters et al., 1975).

Thus it seems possible that bacterial metabolism of ingested nutrients and bile acids within the intestine may contribute not only to the nutritional disturbance but also to the hepatic disease which is an almost universal sequel to intestinal bypass. If this suggestion is confirmed by further investigation, there is a prospect of rational treatment or prophylaxis for the major complication of jejuno-ileal bypass surgery.

Acknowledgements

We thank Mr J.-C. Gazet and Professor T. R. E. Pilkington for permission to study their patients; Professor H. P. Lambert and Dr T. C. Northfield for advice and encouragement; Dr Jennifer Nisbet, Mrs Lisa Ang and Mr Robert Bird for invaluable technical assistance; and Mr Martin Bland for statistical advice. The study was partly supported by the St George's Hospital Research Fund.

References

BARRY R. E., CHOW A. W. and BILLESDON J. (1977) Role of intestinal microflora in colonic pseudo-obstruction complicating jejuno-ileal bypass. *Gut* **18**, 356–359.

BROWN R. G., O'LEARY J. P. and WOODWARD E. R. (1974) Hepatic effects of jejuno-ileal bypass for morbid obesity. *Am. J. Surg.* **127**, 53–58.

CAREY J. B., WILSON I. D., ZAKI F. G. et al. (1966) The metabolism of bile acids with special reference to liver injury. *Medicine* **45**, 461–470.

COWAN S. T. and STEEL K. J. (1974) *Manual for the Identification of Medical Bacteria*, 2nd ed. Cambridge, Cambridge University Press.

CURZON G. and WALSH J. (1962) A method for the determination of urinary indoxyl sulphate (indican). *Clin. Chim. Acta* **7**, 657–663.

DANO P., LENZ K. and JUSTESEN R. (1974) Bile acid metabolism and intestinal bacterial flora after three types of intestinal shunt operation for obesity. *Scand. J. Gastroenterol.* **9**, 767–774.

DONALDSON R. M. (1965) Studies on the pathogenesis of steatorrhoea in the blind loop syndrome. *J. Clin. Invest.* **44**, 1815–1825.

DRASAR B. F. and HILL M. J. (1974) *Human Intestinal Flora*. London, Academic Press.

ENEROTH P. (1963) Thin-layer chromatography of bile acids. *J. Lipid Res.* **4**, 11–16.

HOLDERMAN L. V. and MOORE W. E. C. (1972) *Anaerobe Laboratory Manual*. Anaerobe Laboratory, Blacksburgh, Virginia, USA.

HOLLENBECK J., O'LEARY J. P., MAHER J. W. et al. (1975) An etiologic basis for fatty liver after jejunoileal bypass. *J. Surg. Res.* **18**, 83–89.

JAMES O. F. W., AGNEW J. E. and BOUCHIER I. A. D. (1973) Assessment of the ^{14}C-glycocholic acid breath test. *Br. Med. J.* **3**, 191–195.

KRISTENSEN M., LENZ K., NIELSON O. V. et al. (1974) Short bowel syndrome following resection for Crohn's disease. *Scand. J. Gastroenterol.* **9**, 559–565.

LIEBER C. S. (1974) Effects of ethanol upon lipid metabolism. *Lipids* **9**, 103–116.

MCCLELLAND R. N., DESHAZO C. V., HEIMBACH D. M. et al. (1970) Prevention of hepatic injury after jejunoileal bypass by supplemental jejunostomy feedings. *Surg. Forum* **21**, 368–370.

MAXWELL J. D., SANDERSON I., BUTLER W. H. et al. (1977) Hepatic structure and function after modified jejunoileal bypass surgery for obesity. *Br. Med. J.* **2**, 726–729.

MEZEY E., IMBEMBO A. L., POTTER J. J. et al. (1975) Endogenous ethanol production and hepatic disease following jejunoileal bypass for morbid obesity. *Am. J. Clin. Nutr.* **28**, 1277–1283.

MOXLEY R. T., POZEFSKY T. and LOCKWOOD D. H. (1974) Protein nutrition and liver disease after jejunoileal bypass for morbid obesity. *N. Engl. J. Med.* **290**, 921–926.

PETERS R. L., GAY T. and REYNOLDS T. B. (1975) Postjejunoileal-bypass hepatic disease. Its similarity to alcoholic hepatic disease. *Am. J. Clin. Pathol.* **63**, 318–331.

RUTTER K. R. P., CLEEVE H. and MAXWELL J. D. (1978) Comparison of small intestinal bypass and equivalent small bowel resection on body weight and liver function in the Wistar rat. *Gut* **19**, A454.

SALMON P. A. and REEDYK L. (1975) Fatty metamorphosis in patients with jejunoileal bypass. *Surg. Gynecol. Obstet.* **141**, 75–84.

SHEER H. P., NAIR P. P., WHITE J. J. et al. (1974) Bile acid metabolism and hepatic disease following small bowel bypass for obesity. *Am. J. Clin. Nutr.* **27**, 1369–1379.

WANDS J. R., LA MONT J. T., MANN E. et al. (1976) Arthritis associated with intestinal bypass procedure for morbid obesity. *N. Engl. J. Med.* **294**, 121–124.

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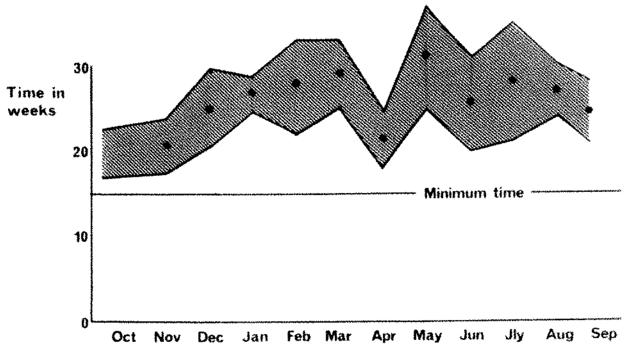

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The effect of bile acids on colonic myoelectrical activity

M. FLYNN, C. DARBY, J. HYLAND, P. HAMMOND AND I. TAYLOR*

SUMMARY

The effect of different concentrations of sodium cholate, sodium chenodeoxycholate and sodium deoxycholate on colonic myoelectrical activity was studied in 4 dogs. There was no statistically significant difference in percentage motility, motility index, basal pressure or mean slow wave frequency with either cholic or chenodeoxycholic acid (5–15 mM). Deoxycholic acid (15 mM), however, caused a marked increase in percentage motility (median control value 4·1, range 0–23; after installation, median value 27·0, range 20·6–45·0, P<0·001). This was accompanied by an increase in spike activity, but no alteration in mean slow wave frequency or basal pressure was seen. Cholestyramine inhibited the motor response. It appears that only deoxycholic acid affects both motility and absorption, presumably by different pathways, and may thus assume importance in disorders of colonic motility.

THE role of bile acids as an aetiological factor in the disorders of colonic motility remains controversial. The enterohepatic circulation ensures that bile acids secreted by the liver are absorbed from the small intestine and only small amounts of chenodeoxycholic and cholic acid enter the colon. It is well known that after extensive small bowel resection increased amounts of bile acids reach the colon and the resultant watery diarrhoea which occurs has been explained by decreased absorption of sodium, bicarbonate and water mediated through cyclic AMP (Hafkenschild, 1977). This sequence can be prevented by cholestyramine (Duncombe et al., 1977).

Diarrhoea frequently occurs in motor disorders of the colon, particularly in the irritable colon syndrome. However, the relationship between bile acids and motor function rather than absorptive function is not clear. Early reports suggested that bile acids inhibited contractions of isolated smooth muscle strips (Schwartz and Magerl, 1924), whereas *in vivo* they produced stimulation (Haney et al., 1939). Kirwan et al. (1975) described increased motility with sodium glycocholate and sodium deoxycholate in rabbits and sodium chenodeoxycholate and sodium taurocholate in man. Other workers suggested that primary bile acids have no significant effect on colonic motility (Falconer et al., 1978).

In this study we have measured the effects of the sodium salts of free bile acids (cholic, chenodeoxycholic and deoxycholic) on colonic motility in the dog. Initial studies have shown that the myoelectrical function of dog colon is similar to that in man. The effect of varying concentrations of each bile acid was assessed.

Materials and methods

Four dogs were studied (weight 15–20 kg). Thiry–Vella loops approximately 20 cm long were fashioned in each. Two silver/silver-chloride electrodes were sutured on to the serosa 15 cm apart and similar electrodes were placed proximal and distal to the colonic anastomosis (*Fig.* 1). The electrode wires were implanted subcutaneously so that they could be used for subsequent myoelectrical recordings. All recordings were carried out at least 2 weeks following operation.

The electrodes were connected to smooth muscle amplifiers and slow wave electrical activity recorded on a Devices pen recorder with an indifferent electrode on the left thigh.

Intraluminal pressure was recorded using a thin open-ended tube (1 mm internal diameter) placed within the loop. Modified Foley catheters ensured that the loop did not leak (*Fig.* 1). The tube was constantly perfused with 0·15 M saline at a rate of 0·2 ml/min using a perfusion pump. Pressure recordings were continuously displayed on the pen recorder.

Control recordings were performed before each experiment by introducing 5 ml of normal saline into the loop for a 30-min period. The following parameters were noted.

1. Pressure: (*a*) mean basal pressure (mmHg); (*b*) percentage motility—the proportion of recording time during which pressure waves were present.
2. Electrical activity: the mean slow wave frequency was recorded as well as the incidence of action potentials.

Following control recordings, the effect of varying pH and motility was noted by introducing 0·15 M phosphate-buffered saline at different pH values (6–10) into the loop and noting the responses. The osmolality of all bile acid solutions was comparable with 0·15 M saline.

Test solutions

Five-millilitre solutions of sodium deoxycholate, sodium cholate and sodium chenodeoxycholic (Maybridge Chemicals) were used in the study. Concentrations of between 5 and 15 mM were used and each solution was in the loop for a minimum of 20 min. The order was randomized for each experiment. At least two studies at each concentration were performed on different days in each dog.

The results for motility were calculated and analysed by non-parametric methods (Wilcoxon rank sum tests and area under standard curves).

Results

Control studies

The median percentage motility in the control studies was 9·0 per cent (range 0–50·0 mmHg). There was no statistically significant increase in motility following the introduction of solutions with varying pH.

Two slow wave electrical rhythms were recorded from the loop. The predominant one had a mean frequency of 0·215 ± 0·027 Hz (12·9 ± 1·6 c/m). The other had a slower frequency, 0·122 ± 0·005 Hz (7·3 ± 0·3 c/m) (*Fig.* 2). These mean frequencies were lower than those recorded from the proximal anastomosed colon—0·245 Hz (14·7 c/m) and 0·130 Hz (7·8 c/m)—reflecting the effect of transection on slow wave frequency.

Bile acids

Cholic and chenodeoxycholic acids: These bile acids produced no statistically significant increase in motility in the loop at concentrations of between 5 and 25 mM. The mean percentage motility following installation of each solution is shown in *Table I*.

The mean volume of each solution at the completion of the study was 5·5 ml. There was no statistically significant alteration in the mean slow wave frequency

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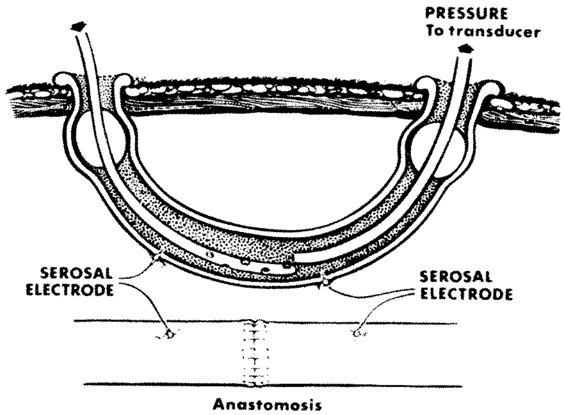

Fig. 1. Diagrammatic representation of Thiry–Vella loops in the dog showing the position of the serosal electrodes.

of either electrical rhythm and no increase in the incidence of action potentials.

Deoxycholic acid

Five and 10 mM deoxycholic acid had no statistically significant effect on motility. However, when given at a concentration of 15 mM there was a statistically significant increase in percentage motility ($P<0{\cdot}001$) (control, median 4·1 per cent, range 0–23 per cent; bile acids, median 27 per cent, range 20·6–45 per cent). The increase in motility occurred on each occasion (*Fig.* 3) and ceased on removal of the solution. This effect was inhibited by cholestyramine. The mean values are shown in *Table I*. The increase in motility had an onset time of 8–13 min and a duration of over 2 h.

There was no alteration in incidence or frequency of either electrical rhythm. Similarly, the increase in motility did not coincide with either rhythm but was noted when either was present. The incidence of action potentials increased and corresponded with the pressure waves (*Fig.* 3). There was no alteration in either slow wave frequency or action potentials in the proximal and distal anastomosed colon.

The colon was removed at the completion of each study and histological preparations showed no structural change in either mucosa or underlying smooth muscle.

Discussion

The efficient enterohepatic circulation allows only 5 per cent (approximately 700 mg) of bile acids to enter the colon each day (Samuel et al., 1968). In the colon anaerobic bacteria change the primary bile acids (cholic and chenodeoxycholic) into secondary forms (deoxycholic and lithocholic) by deconjugation and 7α-dehydroxylation. In the dog colon the dexoycholic acid concentration varies between 5 and 11 mM (in man between 5 and 15 mM).

Increased levels of these bile acids result in watery diarrhoea which could be due both to inhibition of Na^+/K^+ ATPase which reduces absorption of Na^+ ions and water, or to stimulation of cyclic AMP which increases secretion of water and electrolytes. The mechanism is analogous to the effects of cholera enterotoxin and prostaglandins (Conley et al., 1976; Hafkenschild, 1977).

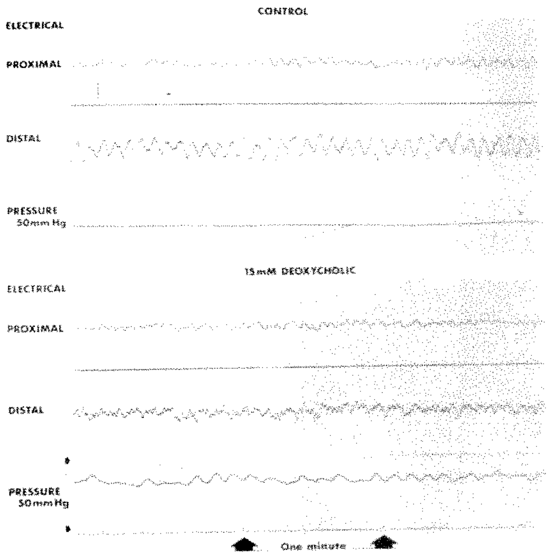

Fig. 2. Recordings of myoelectrical acitivity from the 'loop'. Top trace shows the control recording with a mean frequency of 12·1 c/m. Following the introduction of 15 mM deoxycholic acid into the loop the slow wave frequency is unaltered but action potentials are increased and the percentage motility correspondingly rises.

Table I: EFFECT OF BILE ACIDS ON PERCENTAGE MOTILITY

	Percentage motility	
Concentration	Median	Range
Cholic acid		
Control	12·5	0–50·0
5 mM	5·5	0–56·0 (n.s.)
10 mM	12·1	0–46·0 (n.s.)
15 mM	5·9	0–28·0 (n.s.)
Chenodeoxycholic acid		
Control	11·1	0–17·1
5 mM	4·5	0–9·0 (n.s.)
10 mM	0·8	0–15·8 (n.s.)
15 mM	4·5	0–22·0 (n.s.)
Deoxycholic acid		
Control	4·1	0–23·0
5 mM	13·6	0–35·0 (n.s.)
10 mM	8·6	0–22·0 (n.s.)
15 mM	27·0	20·6–45·0*

* $P<0{\cdot}001$.

Diarrhoea is a common symptom in motor disorders of the colon (particularly the irritable colon syndrome) and it may be that high levels of bile acids are a causative factor. If this is so, the absorptive effects of bile acids on the colon could explain the symptom of diarrhoea. Nevertheless, there is a myoelectrical disturbance in these patients (Taylor et al., 1978) and the role of bile acids in contributing to this motility abnormality has been investigated.

In our studies deoxycholic acid was the only bile acid shown to have a significant effect on colonic motility: indeed, this was seen to occur only at a concentration of 15 mM. However, all three bile acids (cholic, deoxycholic and chenodeoxycholic) have a definite inhibitory effect on absorption (Mekihjian and Phillips, 1970). It has been suggested that any

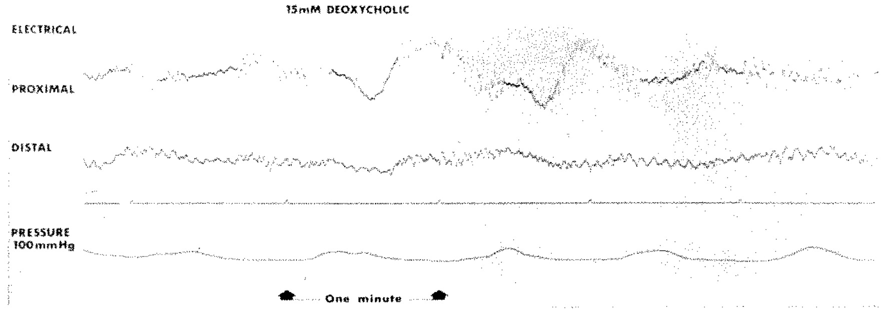

Fig. 3. Myoelectrical recording from the loop following the introduction of 15 mM deoxycholic acid. Note the significant increase in the incidence of action potentials and the corresponding pressure waves.

motor effect is secondary to the increase in intraluminal volume created by this inhibitory effect on absorption. This seems unlikely for two reasons: first, the change in volume created by 5–15-mM concentrations of bile acid was less than 10 per cent, which would not create such a large increase in motility, and secondly, if this were the entire explanation, all bile acids should have a similar action to 15 mM deoxycholic acid.

The increase in motility created by deoxycholic acid could be due to effects on the action of neurotransmitters of colonic smooth muscle either by an inhibitory effect at adrenergic sites or by enhancement of the action of acetylcholine on colonic smooth muscle. Falconer et al. (1978) suggest that deoxycholic acid stimulates smooth muscle contraction by mediating the release of prostaglandin E_2, and this effect can be inhibited by indomethacin. However, indomethacin has inhibitory effects on 5-hydroxytryptamine, bradykinin and histamine as well as prostaglandin E_2 (Sorrentino et al., 1972) and any of these compounds could be released by deoxycholic acid. Furthermore, the inhibitory action of indomethacin on smooth muscle has been interpreted in terms of inhibited Ca^{2+} ion uptake (Northover, 1971), possibly indicating that indomethacin inhibition of PGE_2 biosynthesis is secondary to its inhibition of smooth muscle contractions.

Deoxycholic acid may increase motility by increasing intracellular Ca^{2+} concentrations since slow waves and superimposed action potentials (or spikes) are dependent on Ca^{2+} ion levels (Grundfest, 1976). Evidence from studies on chick small intestine indicates that bile acids increase calcium ion absorption (Webling and Holdsworth, 1965) and work on rats suggests that Ca^{2+} ion absorption can be increased in the colon (Harrison and Harrison, 1969; Petith and Schedl, 1976).

Increased calcium absorption following the action of deoxycholic acid may occur in a number of ways:

1. By increasing membrane permeability in a similar way to acetylcholine (Szursewski, 1973).
2. By inhibition of an electrogenic calcium pump. Deoxycholic acid, unlike the primary bile acids, will effect Mg^{2+}-dependent ATPase and Mg^{2+} absorption is similar to that of Ca^{2+} (Hafkenschild, 1977).
3. By increasing the solubility of insoluble calcium salts found in the colon.
4. By binding Ca^{2+} ions and entering the cell as a calcium–bile acid complex.

Further studies are now being undertaken on Ca^{2+} absorption and bile acids in the colon.

It thus appears that any effect of bile acids on colonic motility is specific to deoxycholic acid at a slightly higher level than normal physiological concentrations. This response appears to be an 'all or nothing relationship' in that concentrations of less than 15 mM have no significant effect on motility whereas concentrations greater than this cause an increase in motility. This may explain some of the features encountered in motor disorders of the colon.

References

CONLEY D. R., COYNE M. J., BONORRIS G. G. et al. (1976) Bile acid stimulation of colonic adenylate cyclose and secretion in the rabbit. *Dig. Dis.* **21**, 453–458.

DUNCOMBE V. M., BOLIN T. D. and DAVID A. E. (1977) Double blind trial of cholestyramine in post-vagotomy diarrhoea. *Gut* **18**, 531–535.

FALCONER J. D., SMITH A. M. and EASTWOOD M. A. (1978) Effect of bile salts and prostaglandins on colonic motility in the rabbit. In: DUTHIE H. L. (ed.) *Gastrointestinal Motility in Health and Disease.* Lancaster, MTP Press, pp. 607–615.

GRUNDFEST H. (1976) The role of calcium ions in extraction–concentration coupling. In: BULBRING E. and SCHUBA M. F. (ed.) *Physiology of Smooth Muscle.* New York, Raven Press, pp. 163–174.

HAFKENSCHILD J. C. M. (1977) Influence of bile acids on the (Na^+/K^+)-activated and Mg^{2+}-activated ATPase of rat colon. *Pflügers Arch.* **369**, 203–206.

HANEY H. F., ROLEY W. C. and COLE P. A. (1939) The effect of bile on the propulsive motility of Thiry–Vella loops in dogs. *Am. J. Physiol.* **125**, 82–88.

HARRISON H. C. and HARRISON H. E. (1969) Calcium transport by rat colon *in vivo. Am. J. Physiol.* **217**, 212–225.

KIRWAN W. O., SMITH A. N., FALCONER J. D. et al. (1975) Bile acids and colonic motility in the rabbit and the human. *Gut* **16**, 894–902.

KUNZE M. and VORGTE W. (1971) Significance of phospholipase A for prostaglandin formation. *Ann. NY Acad. Sci.* **180**, 123–125.

MEKIHJIAN M. S. and PHILLIPS S. F. (1970) Perfusion of the canine colon with unconjugated bile acids. *Gastroenterology* **59**, 120–129.

NORTHOVER B. J. (1971) Mechanism of inhibitory action of indomethacin on smooth muscle. *Br. J. Pharmacol.* **41**, 540–541.

PETITH M. M. and SCHEDL H. P. (1976) Intestinal adaptation to dietary calcium restriction: *in vivo* cecal and colonic calcium transport in the rat. *Gastroenterology* **71**, 1039–1042.

SAMUEL P., SAYPOL G. M., MEILMAN E. et al. (1968) Absorption of bile acids from the large bowel in man. *J. Clin. Invest.* **47**, 2070–2078.

SCHWARTZ C. and MAGERL C. (1924) Beiträge zur Physiologie der Verdauung: 7. Uber den Einfluss von Galle und Zucker auf den Tonus und die Pendelbeuregungen des überlebenden Katzendarmes. *Pflügers Arch. Ges. Physiol.* **202**, 509-522.

SORRENTINO L., CAPASSO F. and DI ROSA M. (1972) Indomethacin and prostaglandins. *Eur. J. Pharmacol.* **17**, 306–308.

SZURSZEWSKI J. H. and BULBRING E. (1973) The stimulant action of acetylcholine and catecholamines on the uterus. *Philos. Trans. R. Soc. Lond.* (*Biol. Sci.*) **265**, 149.

TAYLOR I., DARBY C., HAMMOND P. et al. (1978) Is there a myoelectrical abnormality in the irritable colon syndrome? *Gut* **19**, 391–395.

WEBLING D. D. A. and HOLDSWORTH E. S. (1965) The effect of bile, bile acids and detergents on calcium absorption in the chick. *Biochem. J.* **97**, 408–421.

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Reversed rotation of the mid gut: case reports

K. M. DESAI*

Case 1: A 64-year-old woman presented on 18 July 1978 with a clinical and radiological picture suggestive of caecal volvulus (*Fig.* 1). Laparotomy revealed a clockwise volvulus of the caecum and ascending colon through 360°. It was untwisted and the large bowel distal to the hepatic flexure pursued a course along the posterior abdominal wall dorsal to the small intestine and its mesentery to the origin of the superior mesenteric artery, to reappear in the left upper quadrant of the abdomen, where the left side of the transverse colon was in its normal relationship to the stomach and great omentum. Beyond this point the large bowel pursued a normal course. The great omentum passed direct from the stomach to become adherent over loops of small bowel. The descending portion of the duodenum passed straight down into the jejunum in front of the origin of the superior mesenteric artery. After deflation and derotation the bowel was returned to the abdomen. The patient made an uneventful recovery.

Case 2: A 79-year-old man was admitted to hospital as an emergency on 31 December 1949 with evidence of spreading lower abdominal peritonitis. At laparotomy the peritonitis was found to be due to perforated sigmoid diverticulitis. The treatment proposed was peritoneal toilet and drainage, with defunctioning transverse colostomy, but the transverse colon could not be found in the normal position. Further exploration revealed anatomy similar to that of *Case* 1. The splenic flexure was normally located, but the transverse colon ran posterior to the duodenojejunal junction and the superior mesenteric artery. The great omentum, devoid of colon, passed straight from the greater curvature of the stomach to lie over the small bowel. A diagnosis of reversed mid gut rotation was made and colostomy was omitted. The patient died of a cerebrovascular accident on the third postoperative day.

Anomalous intestinal rotation has been well documented by various authors including Dott (1923), Haymond and Dragstedt (1931), Gardner and Hart (1934), McIntosh and Donovan (1939) and Snyder and Chaffin (1954). Reversed rotation is rare. Davies et al., in a review article in 1955, found only 31 cases in the literature. In 7 of these the anomalous rotation was encountered incidentally at laparotomy for other conditions or at post-mortem: the other 24 had presented as intestinal obstruction. Wang and Welch (1963), reviewing 50 cases of abnormal rotation, cited only one instance of reversed rotation.

Acknowledgements
I am grateful to Mr E. G. Hardy, Consultant Surgeon, Chester Royal Infirmary, for providing me with details of the second case and for his inspiration and constructive criticism in preparing this paper. My sincere thanks also to Miss Mary Plant and Mrs Barbara King for their secretarial help.

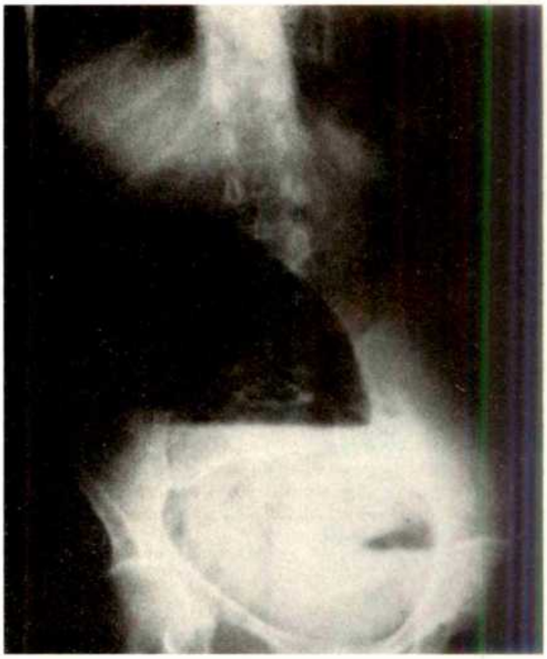

Fig. 1.

References

DAVIES O., JOHANSEN R. and GOLDMAN L. (1955) Reversed rotation of the bowel causing acute intestinal obstruction. *Ann. Surg.* **142**, 875–897.

DOTT N. M. (1923) Anomalies of intestinal rotation: their embryology and surgical aspects. *Br. J. Surg.* **11**, 251–286.

GARDNER C. E. and HART D. (1934) Anomalies of intestinal rotation as a cause of intestinal obstruction. *Arch. Surg.* **29**, 942–981.

HAYMOND H. E. and DRAGSTEDT L. R. (1931) Anomalies of intestinal rotation. *Surg. Gynecol. Obstet.* **53**, 316–329.

MCINTOSH R. and DONOVAN E. J. (1939) Disturbance of rotation of the intestinal tract. *Am. J. Dis. Child.* **57**, 116–166.

MALL F. P. (1898) Development of the human intestine and its position in the adult. *Johns Hopkins Med. Bull.* **9**, 197–208.

SNYDER W. H. and CHAFFIN L. (1954) Embryology and pathology of the intestinal tract. *Ann. Surg.* **140**, 368–380.

WANG C. and WELCH C. E. (1963) Anomalies of intestinal rotation in adolescents and adults. *Surgery* **54**, 839–855.

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Chylous ascites and obstructive lymphoedema of the small bowel following abdominal radiotherapy

P. A. HURST AND J. M. EDWARDS*

SUMMARY

The case history of a patient who developed chylous ascites following abdominal irradiation for recurrent carcinoma of the colon is presented. Laparotomy revealed generalized radiation damage of the small bowel with a particularly severely affected segment of jejunum, from the serosal surface of which chyle was seen to be leaking. Mesenteric lymphangiography revealed an obstruction to lymphatic drainage in the mesentery. Resection of the worst affected segment of bowel prevented further development of chylous ascites.

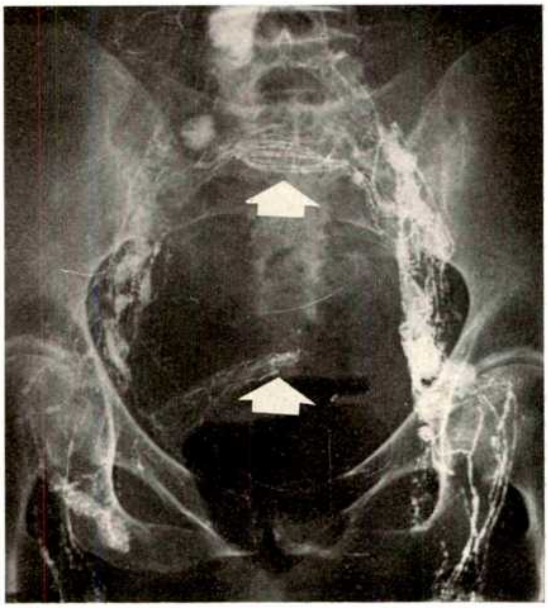

Fig. 1. Bipedal lymphangiogram performed following the development of chylous ascites 18 months after irradiation to the para-aortic nodes. Note the presence of abnormal collateral lymph channels around the bladder and in the presacral area (arrows) indicating proximal lymphatic obstruction. There is no evidence of residual para-aortic nodes or chylous leakage. Two calcified lymph nodes are present in the mesentery.

Case report

A 71-year-old housewife underwent left hemicolectomy for carcinoma of the sigmoid colon (J. M. E.). There were lymphatic metastases up to and including the para-aortic nodes. Histology revealed a well-differentiated adenocarcinoma. Recovery was uneventful and the patient was well until 18 months later when she presented with abdominal pain. On examination there was a palpable mass in the epigastrium and lymphography showed this to be due to secondary tumour in the para-aortic nodes. She received a course of radiotherapy, consisting of 4481 rad to the para-aortic nodes and 4499 rad to the pelvic nodes over 38 days using 8 meV and this was followed by a course of chemotherapy. Methyl CCNU 210 mg stat, 5FU 430 mg daily for 5 days and DIC 100 mg/m^2 daily for 5 days. This regimen was repeated twice at 2-monthly intervals and there was good clinical response with reduction in size of the epigastric mass. However, the patient then developed thrombocytopenia (platelets 10 400 mm^3) and presented as an emergency with gastrointestinal bleeding, passing melaena stools. Her haemoglobin fell to 5·5 g/dl but she responded well to blood transfusion and her bleeding ceased spontaneously. Liver ultrasound and barium enema at this time failed to reveal any residual tumour deposits. She was readmitted 1 month later with a further melaena associated with a haemoglobin level of 5·0 g/dl and a platelet count of 240 000/mm^3. After resuscitation the patient improved but bleeding continued and necessitated laparotomy. At operation gastrotomy was performed and this showed multiple mucosal bleeding points, presumed to be due to radiation gastritis. A high Polya partial gastrectomy was performed. The small bowel was found to be thickened and oedematous but there was no palpable evidence of residual tumour in the para-aortic nodes, nor of metastases in the liver. Her postoperative course was uneventful despite surgery on irradiated tissue.

Three years after hemicolectomy (18 months after radiotherapy), the patient developed ascites and this was initially thought to be malignant. However, paracentesis yielded 2 l of chylous fluid, analysis of which revealed chylomicrons but no malignant cells. Bipedal lymphography (*Fig.* 1) revealed no evidence of para-aortic node involvement. There was evidence of collateral lymphatic pathways (e.g. around the bladder) which had developed, presumably, as a result of proximal lymphatic obstruction.

Following 48 h of high fat diet (to show up chylous leakage) a laparotomy was performed through a right paramedian incision (J. M. E.). There were dense adhesions and most of the small bowel was found to be thickened and oedematous, with serosal telangiectasia and subserosal inclusion chylous cysts. One segment of jejunum was particularly severely involved and distended lymphatics full of chyle were visible on the serosa from which chyle oozed freely (*Fig.* 2).

A mesenteric lymphogram was performed by cannulation of a distended serosal lymphatic and the infusion of Lipiodol Ultra-Fluid (*Fig.* 3). No flow into the lymphatics in the mesentery occurred but back flow of contrast medium filled the lymphatics in the bowel wall (*Fig.* 4). No Lipiodol reached the cisterna or thoracic duct. The lymphatic block was presumably due to radiation fibrosis in the mesentery.

The worst affected segment of jejunum (some 20 cm in length) and its mesentery was resected and the remaining bowel was anastomosed in two layers. Histology of the resected bowel revealed the typical changes of irradiation with submucosal fibrosis, arterial sclerosis and marked lymphatic ectasia (*Fig.* 5). In the year following this operation the ascites has not recurred.

Discussion

The development of chylous ascites following radiation therapy for ovarian carcinoma was reported by Murray and Massey in 1974. They successfully treated 3 cases with medium chain triglyceride diet after excluding recurrent disease at laparotomy. This diet is extremely unpalatable and is poorly tolerated.

The findings at mesenteric lymphangiography in this case confirm the suggestion made by Jackson (1976) that there is obstruction to the normal flow in the mesenteric lymphatics secondary to radiation damage. The backfilling of lymphatics in the bowel wall (*Fig.* 4) may be likened to dermal backflow seen at pedal lymphography in obstructive lymphoedema

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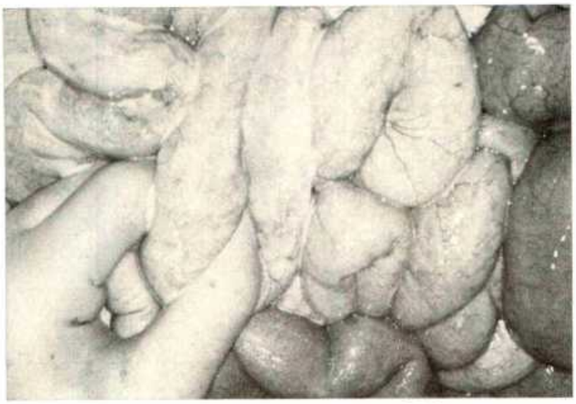

Fig. 2. The most severely affected segment of jejunum, showing chyle leaking from the serosa and post-radiation telangiectasia. Other loops of small bowel are less damaged.

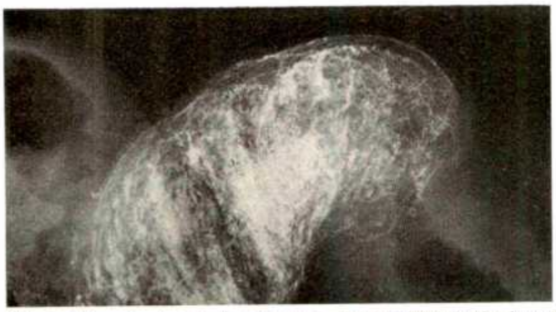

Fig. 3. Mesenteric lymphangiogram. Lymphatics in the bowel wall are filled but there is no filling of mesenteric lymphatics, nor of mesenteric nodes. (The nodes seen are iliac nodes still filled with Lipiodol from previous lymphography and calcified mesenteric nodes.)

of the limbs. A similar mesenteric lymphangiographic appearance was seen by Kinmonth and Cox (1974) in patients with protein-losing enteropathy in primary lymphoedema. They found that these patients leak chyle from the serosal surface of the bowel and that the chylous ascites was markedly improved by surgical excision of the worst affected bowel. Applying the same principles to this case we excised the most severely affected segment of jejunum, and no further chylous ascites has developed 1 year after operation. The histology of the resected bowel showed distended submucosal lymphatics as reported by Warren and Freidman in 1941. This lymphatic distension can be explained on the basis of obstruction to mesenteric lymphatic drainage as revealed by mesenteric lymphangiography.

This case history is of importance in showing that ascites occurring after abdominal radiation may in some instances be due not to malignancy but to lymphatic block in the mesentery. Diagnostic tap should always be performed and if chylous ascites is found laparotomy should follow as resection of severely affected bowel may prevent accumulation of further chylous ascites.

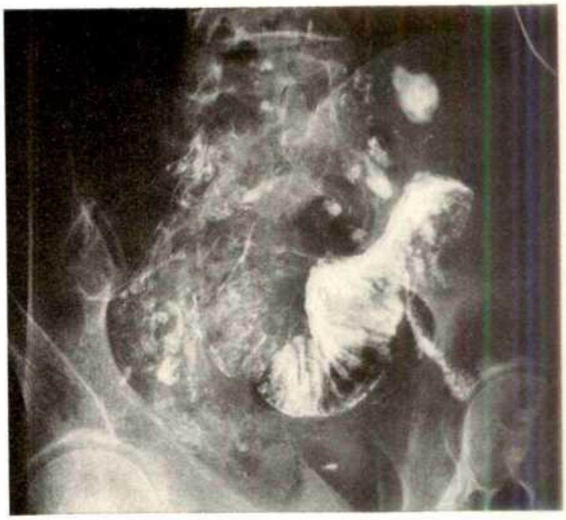

Fig. 4. High definition X-ray of jejunum showing backfilling of lymphatics in the bowel wall due to obstruction of lymphatics in the mesentery.

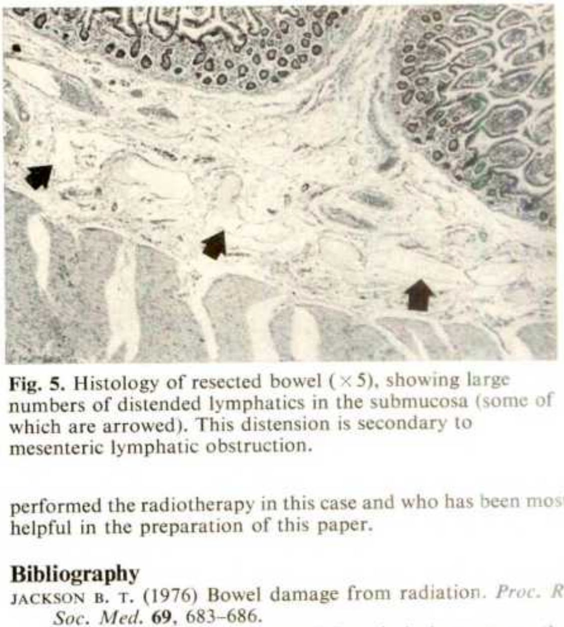

Fig. 5. Histology of resected bowel (× 5), showing large numbers of distended lymphatics in the submucosa (some of which are arrowed). This distension is secondary to mesenteric lymphatic obstruction.

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We would like to thank Dr C. L. Harmer, Consultant in Radiotherapy and Oncology, Royal Marsden Hospital, who performed the radiotherapy in this case and who has been most helpful in the preparation of this paper.

Bibliography

JACKSON B. T. (1976) Bowel damage from radiation. *Proc. R. Soc. Med.* **69**, 683–686.

KINMONTH J. B. and COX S. J. (1974) Protein-losing enteropathy in primary lymphoedema: mesenteric lymphography and gut resection. *Br. J. Surg.* **61**, 589–593.

KINMONTH J. B. and COX S. J. (1975) Protein-losing enteropathy in lymphoedema: surgical investigation and treatment. *J. Cardiovasc. Surg.* **16**, 111–114.

LEVEEN H., CHRISTONDIAS G., MOON I. et al. (1974) Peritoneovenous shunting for ascites. *Ann. Surg.* **180**, 580–591.

MURRAY J. M. and MASSEY F. M. (1974) Chylous ascites after radiation therapy for ovarian carcinoma. *Obstet. Gynecol.* **44**, 749–751.

WARREN S. and FREIDMAN N. (1941) Pathology and pathological diagnosis of radiation lesions in the gastrointestinal tract. *Am. J. Pathol.* **18**, 499–507.

WELLWOOD J. M. and MASSEY F. M. (1963) The intestinal complications of radiotherapy. *Br. J. Surg.* **60**, 814–818.

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Leucocyte counts in the diagnosis and prognosis of acute appendicitis in children

N. V. DORAISWAMY*

SUMMARY

Preoperative total and differential leucocyte counts were made in 225 children with acute appendicitis, 50 children with a normal appendix and 100 children with acute abdominal pain which resolved without any therapy. When adjusted to age, neutrophilia in 96 per cent, 30 per cent and 32 per cent and leucocytosis in 41·8 per cent, 4 per cent and 3 per cent was noted in the respective groups, the levels being significantly higher in the acute appendicitis group than in the other two groups. Among children with appendicitis, infections were observed in 62·8 per cent of the group with leucocytosis and in 13·7 per cent of the group with a normal leucocyte count; the difference is statistically significant. It is suggested that in acute appendicitis neutrophilia supports the diagnosis and leucocytosis indicates the prognosis. The rate of infection increases as the total leucocyte count rises above the upper normal limit. The difference of opinions on the significance of leucocyte counts in acute appendicitis is discussed.

Table I: NORMAL UPPER LIMITS OF LEUCOCYTE COUNTS IN DIFFERENT AGE GROUPS

Age (yr)	Total leucocyte counts/dl	Neutrophils (%)
0–5	15 000	50
5–10	15 000	65
10–15	13 000	75

Table II: RAISED LEUCOCYTE COUNTS IN THE GROUPS STUDIED

		Raised counts	
Group	No. of cases	Total leucocytes	Neutrophil percentage
Acute appendicitis	225	94 (41·8)	216 (96)
Normal appendix	50	2 (4·0)	15 (30)
Abdominal pain	100	3 (3·0)	32 (32)
Total	315	99	263

Figures in brackets are percentages of total patients.

Leucocyte counts are commonly performed during the assessment of patients suspected of having acute appendicitis and the experience recorded here gives an indication of their value in both diagnosis and prognosis.

Patients and methods

Before operation total and differential leucocyte counts were made on 225 children with acute appendicitis, 50 children in whom, following a clinical diagnosis of acute appendicitis, normal appendices without any other inflammatory lesion were found at laparotomy and 100 children with acute abdominal pain and who recovered without any specific therapy. Children between the ages of 5 and 15 were included in this study. The total leucocyte counts were performed using the Coulter cell counter. The incidence of postoperative abdominal infective complications was recorded. Children with extra-abdominal complications were excluded. Student's *t* test was used for statistical analysis of results and the χ^2 test was used for the data in *Table IV*.

Results

Mann's values (1977) for normal leucocyte counts for children of varying ages have been used in this study (*Table I*). The raised total leucocyte counts and neutrophil percentages among the three groups have been tabulated according to age (*Table II*). A raised neutrophil percentage was noted in all children with a raised total leucocyte count and acute appendicitis and, furthermore, in all but 9 of the remaining children with acute appendicitis (and a normal total leucocyte count), i.e. 96 per cent. In the other two groups a raised neutrophil percentage was observed in 30 per cent and 32 per cent respectively.

The postoperative abdominal infection rate was compared in children with appendicitis to examine the relationship to the leucocyte count (*Fig.* 1). The total leucocyte count was raised in 94, 2 and 3 patients in the respective groups (*Table II*). In the appendicitis group as a whole 66 (29·3 per cent) children had abdominal infective complications with clearly recognizable localizing signs. A further 11 children (4·9 per cent) had fever persisting for more than a day and in the absence of evidence for the existence of infection elsewhere, this was attributed to incompletely resolved infection at the appendix site, thus making a total of 77 (34·2 per cent). Two children in the normal appendix group developed wound infection.

Discussion

The diagnosis of acute appendicitis rests mainly on the history and physical signs. Anxiety not to withhold operative treatment for a potentially serious illness weighs justifiably on the side of intervention in doubtful cases. Despite the indication of a strongly suggestive history with supporting physical signs, many series show that the appendix is found to be normal at about one-quarter of operations—28 per cent (Hobson and Rosenman, 1964), 20 per cent (Swink, 1969), 25 per cent (Jacob et al., 1975). There is a need for improvement in accuracy of clinical diagnosis.

Leucocyte counts are usually ordered to support the clinical diagnosis, but different opinions have been expressed on their significance—useful (Lansden, 1963), no specific value (Shepherd, 1968), misleading (Arnot, 1975), little part (Gilmore et al., 1975). In view of these different opinions, this study was undertaken to correlate the practical usefulness of leucocyte counts in acute appendicitis in children.

When leucocyte counts were analysed according to age (Doraiswamy, 1977), neutrophilia was observed in 216 (96 per cent) children with acute appendicitis but in only 15 (30 per cent) and 32 (32 per cent) children in the remaining two groups. Moreover the

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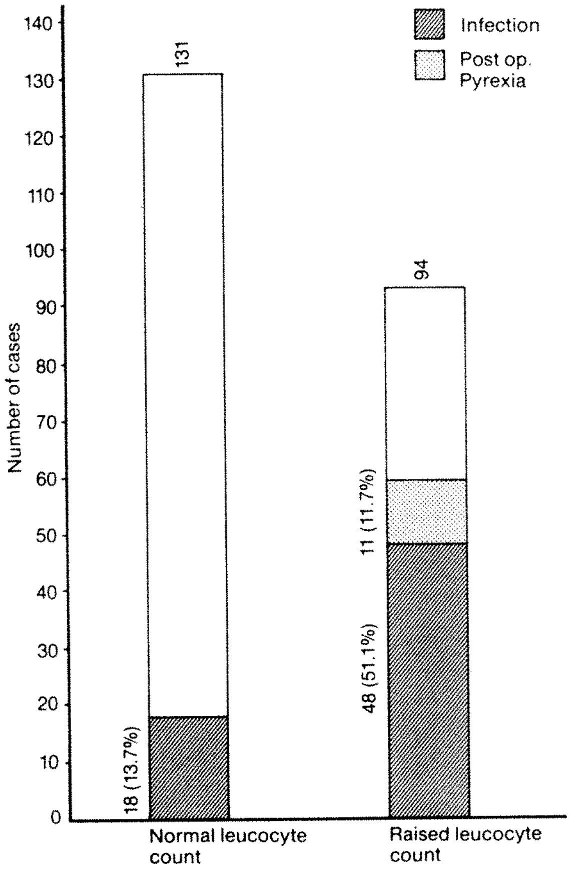

Fig. 1. Incidence of infection according to leucocyte counts in the appendicitis group.

Table III: DETAILED ANALYSIS OF THOSE IN APPENDICITIS GROUP WHO HAD A RAISED TOTAL LEUCOCYTE COUNT

Leucocytes/dl above normal	Inf.	Not inf.	Total
< 1000	3 (1)	12	15 (1)
1001–2000	5 (1)	7	12 (1)
2001–3000	6	5	11
3001–4000	3 (2)	4	7 (2)
4001–5000	6 (2)	2	8 (2)
5001–6000	5 (1)	3	8 (1)
6001–7000	4 (3)	2	6 (3)
7001–8000	2 (1)	—	2 (1)
8001–9000	3	—	3
9001–10 000	5	—	5
> 10 000	6	—	6
Total	48 (11)	35	83 (11)

Table IV: RELATIONSHIP BETWEEN LEUCOCYTOSIS AND INCIDENCE OF INFECTION IN APPENDICITIS GROUP

Leucocytes/dl above normal	Inf.	Not inf.	Total
< 1000	4 (10·04)	12 (5·96)	16
1001–5000	25 (26·99)	18 (16·01)	43
> 5000	30 (21·97)	5 (13·03)	35
Total	59	35	94

Numbers in brackets are expected values.
$\chi^2 + 18{\cdot}05$ with 2 d.f.

results were highly significant ($P < 0{\cdot}001$) when the appendicitis group was compared with the other two groups. They indicate that a raised neutrophil percentage is a useful diagnostic aid to supplement the clinical diagnosis. Conversely, a diagnosis of acute appendicitis should be made with reservations when there is a normal neutrophil percentage. There was no significant difference for neutrophilia between the groups with a normal appendix or abdominal pain.

A significantly ($P < 0{\cdot}001$) raised total leucocyte count was observed in the appendicitis group when compared with the other two groups but there was no significance when the normal appendix group was compared with the abdominal pain group. However, 131 (58·2 per cent) children had a total leucocyte count in the normal range in the appendicitis group and therefore it is not as useful in supplementing the clinical diagnosis as the neutrophil percentage (*Fig.* 1).

The overall incidence of postoperative abdominal infective complications in this series was 34·2 per cent (77 patients) among those in the appendicitis group and 4 per cent in the normal appendix group, similar to the general experience (Editorial, 1971; Gilmore et al., 1975).

When the immunological mechanisms are normal, leucocytes are important for protecting against harmful agents including bacteria. Organisms in the lumen of the appendix (Doraiswamy et al., 1978) cause the infective complications of acute appendicitis (Doraiswamy, 1978) and secondary sepsis is counteracted by leucocytosis. The importance of the total leucocyte count in acute appendicitis is indicated in *Fig.* 1 which shows that among the 94 children who had a raised total leucocyte count, 62·8 per cent (48 + 11 patients) developed postoperative abdominal infective complications whereas only 13·7 per cent (18 patients) had such complications among the 131 children who had a normal total leucocyte count. This suggests that though infection can be met with when the total leucocyte count is normal, the incidence of infection is significantly ($P < 0{\cdot}001$) higher when the count is raised and hence it is a useful indicator of prognosis.

Table III shows that the incidence of infective complications rises in proportion to the leucocyte count. When the total leucocyte count exceeded 7000 cells/dl above the normal upper limit, it was noted that all children developed abdominal infections.

Table IV shows the relationship between the leucocyte count and the departure from the expected incidence of septic complications in acute appendicitis. It can be seen that as the total leucocyte count increases the incidence of infection increases. The χ^2 value is highly significant ($P < 0{\cdot}001$) and indicates that there is a relationship between leucocytosis and infection.

The contradictory opinions that have been expressed regarding the significance of leucocyte counts in the diagnosis of acute appendicitis are to be explained by the fact that most of these other reports were not analysed against the duration of the disease. It has been noted that the laboratory results, including leucocyte counts, differ according to the duration of the disease (Doraiswamy, 1978), raised total leucocyte counts being observed at a later stage of the disease when bacterial infection is established. Pinpointing the exact time of onset of the disease to correlate the prognosis presents a practical difficulty, but leucocyte counts can be made fairly accurately. It is easier to interpret prognosis in accordance with total leucocyte counts which reflect the incidence of bacterial infection than to recognize the exact time of onset and hence the duration of the disease. Moreover, other factors such as obstruction of the lumen of the appendix by faecoliths, administration of antibiotics and the general immunological status may also influence the rate of infection.

Conclusion

In acute appendicitis in children, when account is taken of age-related variation, the neutrophil percentage is raised in most cases and this finding supports a clinical diagnosis. When the neutrophil percentage is normal, however, a diagnosis of appendicitis should be made with reservation. A moderate rise in the total leucocyte count correlates with the incidence of postoperative abdominal infective complications, until at the level of 7000 cells/dl above the upper normal range infection is found constantly.

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References

ARNOT R. S. (1975) Diagnosis of appendicitis. *South Afr. Med. J.* **49**, 458.

DORAISWAMY N. V. (1977) The neutrophil count in childhood acute appendicitis. *Br. J. Surg.* **64**, 342–344.

DORAISWAMY N. V. (1978) Progress of acute appendicitis—a study in children. *Br. J. Surg.* **65**, 877–879.

DORAISWAMY N. V., CURRIE A. B. M. and BRIDGEWATER F. A. J. (1978) Source and sensitivity of bacteria in acute appendicitis in childhood. *J. R. Coll. Surg. Edinb.* **23**, 216–222.

EDITORIAL (1971) Sepsis after appendicectomy. *Lancet* **2**, 195.

GILMORE O. J. A., BRODRIBB A. J. M., BROWETT J. P. et al. (1975) Appendicitis and mimicking conditions. *Lancet* **2**, 421–424.

HOBSON T. and ROSENMAN L. D., (1964) Acute appendicitis—when is it right to be wrong? *Am. J. Surg.* **108**, 306–312.

JACOB E. T., NATHAN N. B. and IUCHTMAN M. (1975) Error rate factor in the management of appendicitis. *Lancet* **2**, 1032.

LANSDEN F. T. (1963) Acute appendicitis in children. *Am. J. Surg.* **106**, 938–942.

MANN J. R. (1977) In: WOOD B. (ed.) *A Paediatric Vade-mecum*, 9th ed. London, Lloyd-Luke, p. 133.

SHEPHERD J. A. (1968) *Surgery of Acute Abdomen*, 2nd ed. Edinburgh, Churchill Livingstone, p. 260.

SWINK R. L. (1969) Five hundred operations for appendicitis. *Am. Surg.* **35**, 149–151.

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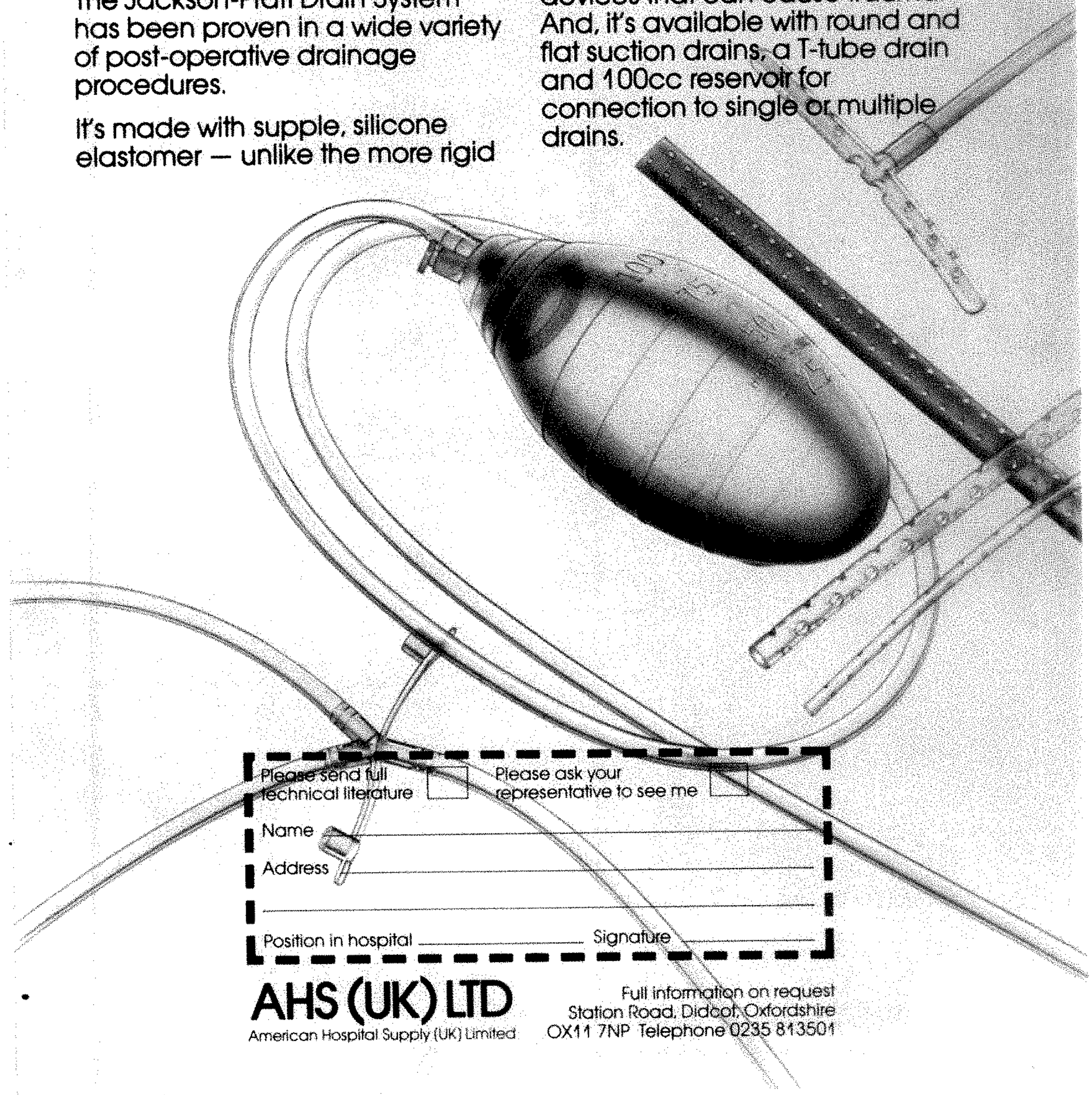

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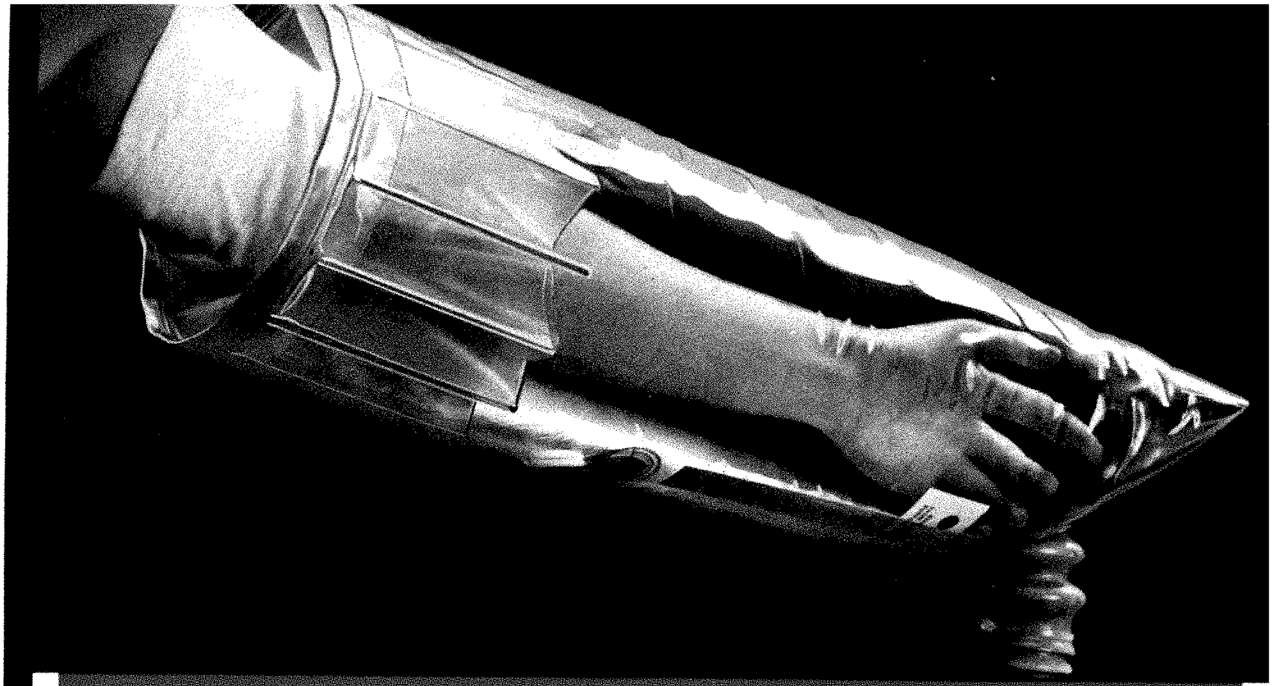

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Br. J. Surg. Vol. 66 (1979) 785–786

Controlled environment therapy in the management of lymphoedema: a case report

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SUMMARY

A case of surgically-treated elephantiasis of a lower limb is reported in which preoperative controlled environment therapy (CET) proved to be an effective, rapid method of reducing the oedema.

Case report

A 67-year-old man presented with a 12-year history of gross swelling of the right lower leg (*Fig.* 1). There were extensive filiform growths of the dorsum of the foot, and *Myobacterium tuberculosis* was grown from a skin biopsy. When referred for surgery he had been on antituberculous chemotherapy for 1 year.

The patient was treated for 2 weeks with CET (Kegal, 1976). The CET machine, designed by the Biomedical Research and Development Unit (BRADU) and available from Cape Engineering Co. Ltd, Warwick, England, allows a limb to be exposed to sterile warm dried air while enclosed in a transparent polyvinyl chloride bag. Cycles of air under pressure are passed through the bag. In this case, the leg was placed in the largest available bag (*Fig.* 2), and exposed to pressures varying from 10 mmHg to 30 mmHg in 15- and 30-s spells, respectively. The treatment was continuous for 2 weeks.

The oedema subsided rapidly, and within a week the maximum calf circumference was reduced from 73 cm to 43 cm. Redundant skin fell posteriorly and formed a convenient fold for wedge excision of skin and subcutaneous tissues. At operation the dorsum of the foot was excised down to the level

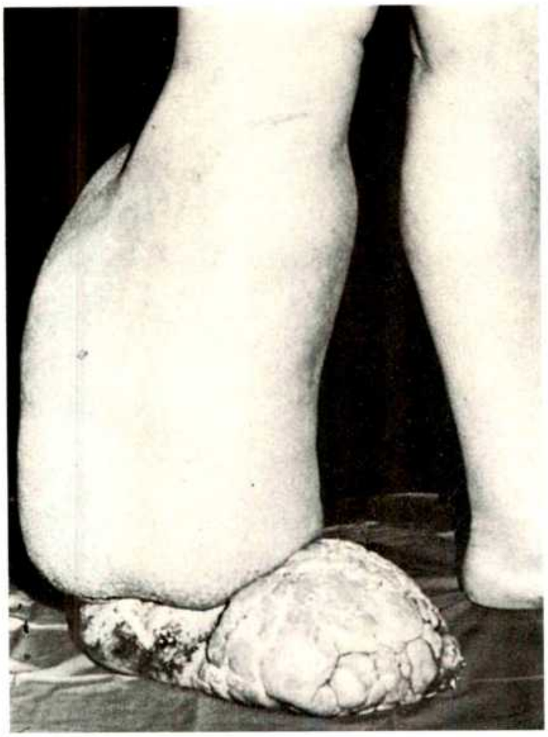

Fig. 1. Gross lymphoedema of the right leg with secondary changes in the foot.

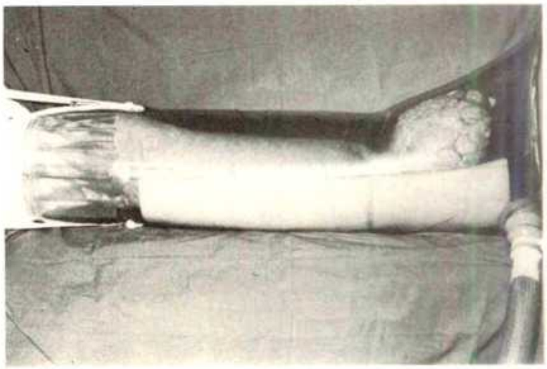

Fig. 2. The leg undergoing controlled environment therapy.

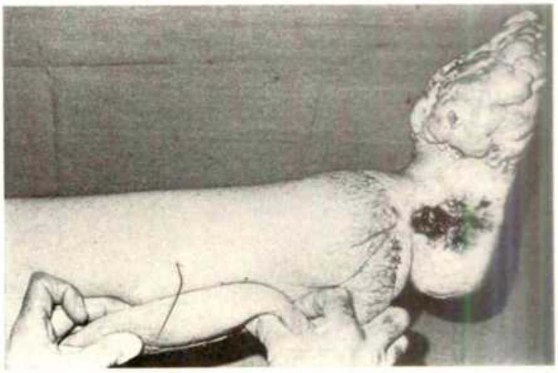

Fig. 3. The reduction of oedema shown after 2 weeks.

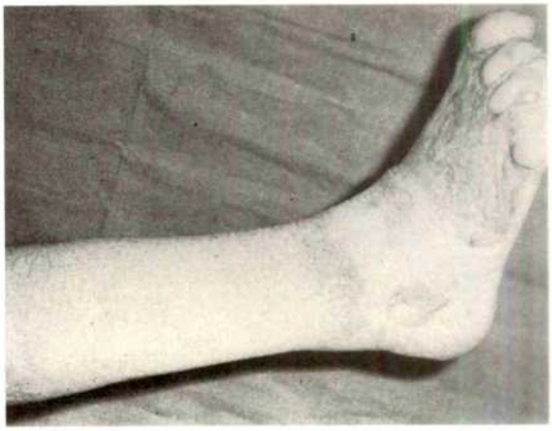

Fig. 4. The result 3 months postoperatively.

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of the extensor tendons. The toes were filleted and the bony skeleton amputated, as there was enlargement of the whole foot. The plantar skin of the toes was turned over to cover the dorsum of the distal forefoot, the remainder of the defect being covered with a split skin graft from the opposite thigh.

Four weeks after operation, CET was used for 10 days to reduce the oedema further, prior to fitting a knee length surgical boot. The quality of the skin graft improved noticeably during CET. The patient has now been symptom-free for 9 months after the operation.

Discussion

Initially developed for use in the limb stump immediately after amputation, CET has been used in many situations where oedema of a limb is a problem. Intermittent pneumatic compression of the lymphooedematous leg has been described before (Calnan et al., 1970; Allenby et al., 1973), but CET apparatus offers added advantages.

1. The limb is visible at all times as the bag is transparent.

2. Physiotherapy can be carried out easily under direct vision.

3. The passage of sterile, warmed, dry air allows great improvement in the condition of the skin.

Postoperatively, the initial result was maintained by continuous compression bandaging and a surgical knee length boot. CET can be included again, if necessary, to reduce any recurrence of oedema very rapidly.

References

ALLENBY F., CALNAN J. S. and PFLUG J. J. (1973) The use of pneumatic compression in the swollen leg. *J. Physiol.* **231**, 65–66.

CALNAN J. S., PFLUG J. J. and MILLS C. J. (1970) Pneumatic intermittent compression legging simulating calf muscle pump. *Lancet* **2**, 502–503.

KEGAL B. (1976) *Phys. Ther.* **56**, 121, 1366–1371.

Paper accepted 8 January 1979.

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A new vascularized bone graft transferred by microvascular anastomosis as a free flap

ROY SANDERS AND BRYAN J. MAYOU*

SUMMARY

We describe a new, versatile bone and soft tissue compound free flap which may be transferred quickly and simply and describe its use in the treatment of compound fracture of the tibia and fibula with non-union due to loss of bone. The iliac crest and overlying soft tissue is transferred to the leg in one stage by microvascular anastomosis of the deep circumflex iliac vessels to vessels in the leg.

OSTEOCYTES lying within the lacunae of conventional bone grafts die (Phemister, 1914; Abbott et al., 1947). If grafting is successful, bone becomes vascularized from its new bed and the lacunae become recolonized. However, if the bone graft is transferred with its own vascular supply, the osteocytes remain viable (Doi et al., 1977). These vascularized bone grafts heal better than the conventional grafts (Doi et al., 1977). However, their use in man has been limited by the availability of suitable donor sites (Taylor et al., 1975; Buncke et al., 1977). We report the use of the iliac crest as a donor site vascularized by the deep circumflex iliac artery. The soft tissues and skin overlying the crest are also supplied by this artery and may be optionally included with the bone.

Case report

A 29-year-old man who sustained a compound fracture of the tibia and fibula 9 months previously was left with a 4-cm bony defect in the middle third of the tibia and a corresponding skin defect and scarring measuring 8 × 6 cm (*Fig.* 1).

A flap of 10 × 8 cm centred over the iliac crest was raised with 4 cm of the crest attached. The origin of the deep circumflex iliac vessels was defined through an incision parallel to and just above the inguinal ligament and by division of the inguinal ligament immediately lateral to the deep external ring. The vessels were traced laterally to the point behind the anterior superior iliac spine where they pierced first the transversalis fascia and then the transversus abdominis muscle to continue along and behind the rim of the iliac crest. After division of the vessels at their origin from the external iliac artery the flap was transferred to fill the leg defect and the deep circumflex iliac vessels were anastomosed end to end to the posterior tibial vessels. These vessels were all about 3 mm in diameter. The skin immediately became pink and the bone bled freely. Postoperatively there was some superficial loss of skin but at no point was the bone exposed. Since the soft tissues were supplied by vessels from the iliac crest, their survival indicated continued vascularization of the graft. There was radiological union of graft and tibia at 4½ months (*Fig.* 2).

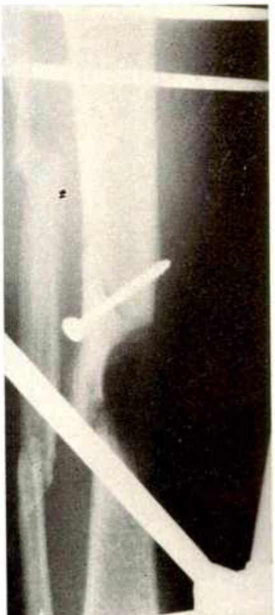

Fig. 1.

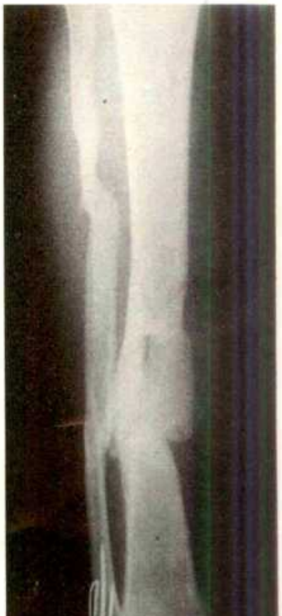

Fig. 2.

Fig. 1. A preoperative radiograph 9 months after injury showing the bones stabilized with Hoffman's external fixation and a bony defect.

Fig. 2. A radiograph of the leg 4½ months after surgery showing radiological union.

Discussion

The iliac crest based on the deep circumflex iliac vessels fulfils most of the requirements for a useful living bone graft. The bone is readily available and may be easily carved to size. The pedicle is long and consistent with vessels of wide diameter (artery 2·6–3·4 mm and vein 2·6–3·5 mm) (Mayou and Sanders, 1978). The soft tissues overlying the crest may be optionally included and the whole flap may be raised quickly and simply. Taylor and Watson (1978) have included the iliac crest with a free groin flap based on the superficial circumflex iliac vessels. However, these superficial vessels give little nourishment to the iliac crest and are of a small diameter (1·4 mm) with a short pedicle (Mayou and Sanders, 1978).

This living bone graft based on the deep circumflex vessels could be used without soft tissues in the treatment of non-union, where there is no bone loss but failure to heal after conventional bone grafting, and also in reconstruction, where bone is required sometimes with and sometimes without soft tissues, such as reconstruction of the mandible in congenital malformation, for gunshot wounds or after cancer extirpation.

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References

ABBOTT L. C., SCHOTTSTAEDT E. R., SAUNDERS J. B. et al. (1947) The evaluation of cortical and cancerous bone as grafting material. *J. Bone Joint Surg.* **29**, 381–414.

BUNCKE H. J., FURNAS D. W., GORDON L. et al. (1977) Free osteocutaneous flap from a rib to the tibia. *Plast. Reconstr. Surg.* **59**, 799–805.

DOI K., TOMINAGA S. and SHIBATA T. (1977) Bone grafts with microvascular anastomoses of vascular pedicles. *J. Bone Joint Surg.* **59A**, 809–815.

MAYOU B. J. and SANDERS R. (1978) A free compound osseocutaneous flap based on the deep circumflex iliac vessels. Paper read to British Association of Plastic Surgeons.

PHEMISTER D. B. (1914) The fate of transplanted bone and regenerative power of its various constituents. *Surg. Gynecol. Obstet.* **19**, 303–333.

TAYLOR G. I., MILLER G. D. H. and HAM F. J. (1975) The free vascularised bone graft. *Plast. Reconstr. Surg.* **55**, 533–544.

TAYLOR G. I. and WATSON N. (1978) One stage repair of compound leg defects. *Plast. Reconstr. Surg.* **61**, 494–506.

Paper accepted 27 July 1979.

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The early diagnosis of ectopic pregnancy

GRAEME J. HUGHES*

SUMMARY

In a survey of 235 consecutive cases of ectopic pregnancy it was found that over 50 per cent were incorrectly diagnosed by the general practitioner and 36 per cent by a hospital doctor. Ten per cent of patients were sent home before the diagnosis was made.

Over 30 per cent of patients were sent to general surgical wards and these patients had different characteristics from those sent to gynaecological wards.

High risk patients can be identified from their past history. The increasing use of the laparoscope has been associated with earlier detection of ectopic pregnancy before the stage of rupture.

THERE is still a significant mortality in patients with ectopic pregnancy, and in the last maternal mortality report (Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1972) 11 of the 34 deaths were considered to be avoidable. The incidence of ectopic pregnancy rose in Aberdeen until 1973 and since then has levelled off with some fluctuations (*Fig.* 1). It is important that all practitioners dealing with the disease should increase their awareness of the pitfalls in diagnosis and be able to identify high risk patients.

Patients and methods

Case notes of all women admitted to Aberdeen hospitals with ectopic pregnancy were studied over the years 1968 to 1977. Patients who had operations performed in non-gynaecological wards were also included in this study. The great majority of women in the Grampian region who had ectopic pregnancy diagnosed were sent to Aberdeen for surgery.

Results

Errors in diagnosis made by general practitioners

The diagnoses were obtained from the general practitioners' referral letters to the hospital. Some patients had no referral letter and others had no specific diagnosis mentioned (*Table I*).

The provisional diagnosis of ectopic pregnancy was only suggested in a minority of cases, and 1 in 5 patients was not even sent to a gynaecological ward. The initial diagnosis of the general practitioner was very important because it determined where the patient should be sent, and that in turn had a bearing on the type of investigation and treatment carried out. Some patients (19 per cent) were sent as non-emergencies to outpatient departments, sometimes surgical but usually gynaecological, for further assessment. Over 30 per cent were sent to surgical wards as emergencies. Three cases went to medical wards.

The incorrect provisional diagnoses made by the general practitioners are set out in *Table II*.

Errors in diagnosis at the outpatient department

Of those 44 patients who went to the outpatient department, 16 were not admitted as emergencies although most of them were given admission dates for further investigation.

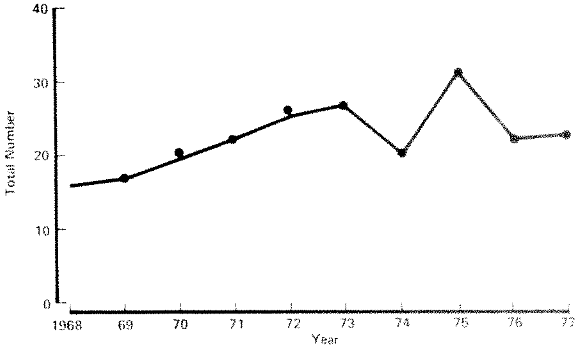

Fig. 1. Incidence of ectopic pregnancy 1968–77.

Errors in diagnosis after admission to hospital

The diagnoses shown in *Tables III* and *IV* were made prior to anaesthetic but with the aid of non-surgical investigations.

Almost 10 per cent of patients were sent home before the diagnosis of ectopic pregnancy was made, often having had a curettage for suspected incomplete or missed abortion. Occasionally the patients were recalled when histological examination of the curettings showed the Arias Stella reaction (florid secretory endometrium, typical of early pregnancy), but most returned with a ruptured ectopic pregnancy in a state of shock.

The type of wrong diagnosis depended on the ward to which the patient was sent. The common misdiagnosis in those sent to a gynaecological ward was spontaneous abortion or ovarian cyst, and in those sent to a surgical ward, appendicitis. Moreover, those women sent to surgical wards had different characteristics from those who were sent to gynaecological wards (*Table V*).

If the patient had an acute abdomen the general practitioner felt safer to admit her to a surgical ward, so most of the patients sent to surgical wards had ruptured ectopics and in most the ectopic was on the right side, giving the impression that it was appendicitis. Not surprisingly the correct diagnosis was more likely to be made if the patient had been admitted to a gynaecological ward than if the patient had been sent to a surgical ward.

Fig. 2 shows that the preoperative diagnosis of ectopic pregnancy is not becoming easier, probably because there are few non-surgical techniques to give much help.

Identifying the high risk group

Over 60 per cent of the patients in this series had one or more factors in their past history which are known to be associated with ectopic pregnancy.

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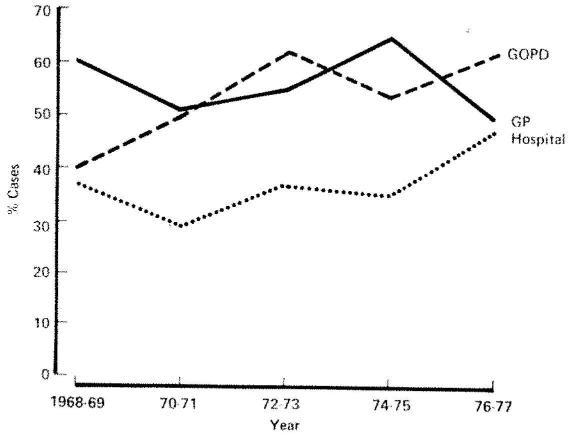


Fig. 2. Trends in preoperative diagnosis of ectopic pregnancy.

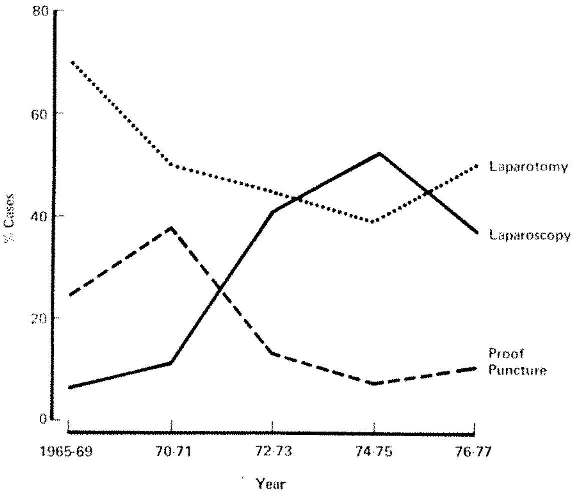


Fig. 3. Use of various investigations in diagnosis of ectopic pregnancy.

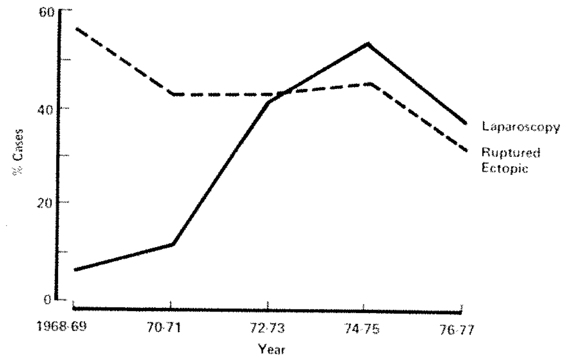


Fig. 4. Impact of laparoscopy on ectopic pregnancy.

The mean age in our series was 28. Previously it has been a disease of the third and fourth decades but more recently the mean age has been decreasing, and there were a surprising number of teenage girls. In 1968–9 36 per cent were older than 35 years, whereas

Table I: GENERAL PRACTITIONERS' DIAGNOSIS
(*n* = 191)

Possible ectopic	83 (43·5%)
Other gynaecological	66 (34·6%)
Non-gynaecological	42 (21·9%)

Table II: INCORRECT DIAGNOSES MADE BY GENERAL PRACTITIONERS

	Gynaecological	Non-gynaecological
Spontaneous abortion	38	
Ovarian cyst	10	
Pelvic sepsis	9	
Dysfunctional bleeding	5	
Referred for termination	2	
Prolapse	1	
Infertility	1	
Appendicitis		17
Acute abdomen		7
Urinary infection		5
Mild abdominal pain		4
Constipation		3
Diarrhoea		3
Cholecystitis		2
Aneurysm		1
Diverticulitis		1
Perforated ulcer		1
Renal colic		1

Table III: PREOPERATIVE HOSPITAL DIAGNOSIS
(*n* = 226)

Definite ectopic	37 (16·2%)
Possible ectopic	106 (47·1%)
Incorrect diagnosis	83 (36·7%)
Sent home	22 (9·7%)

Table IV: MISTAKES IN DIAGNOSIS MADE AT HOSPITAL

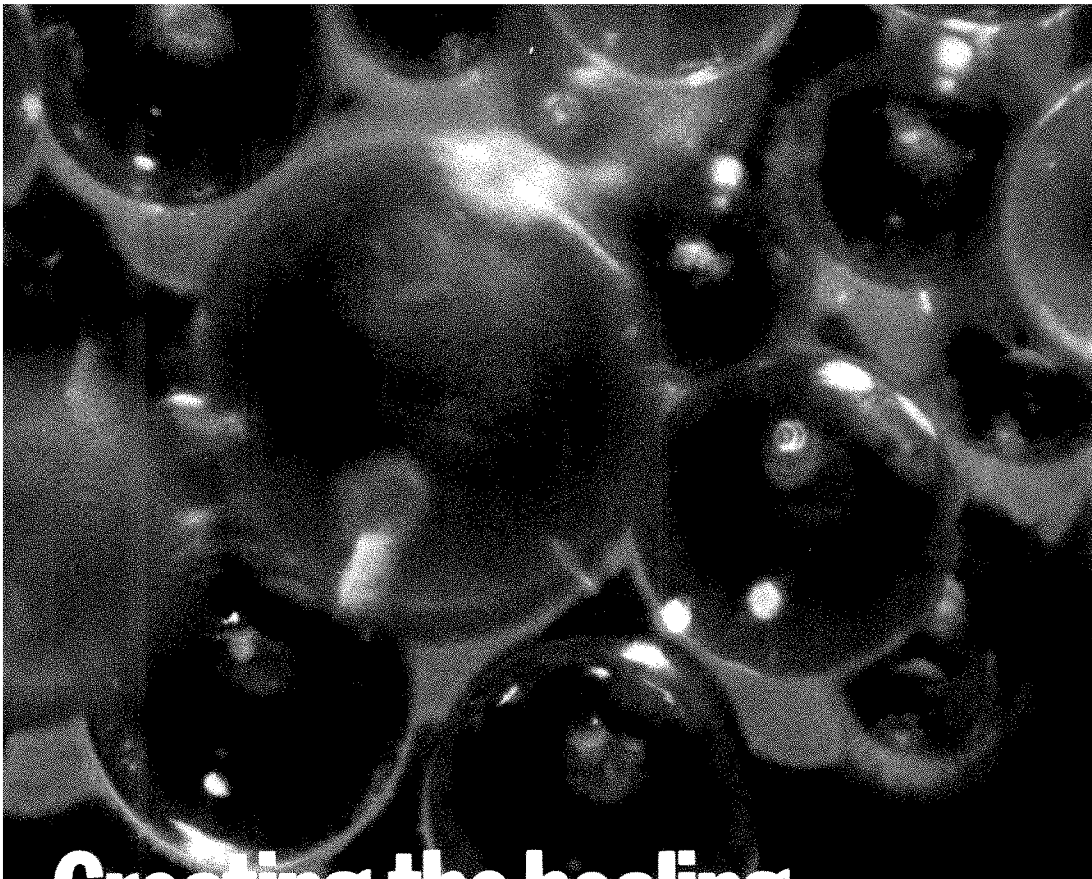
	Gynaecological	Non-gynaecological
Spontaneous abortion	25	
Ovarian cyst	11	
Pelvic sepsis	11	
Dysfunctional bleeding	5	
Endometriosis	2	
Appendicitis		9
Diverticulitis		2
Ureteric colic		2
Myocardial infarction		1
Cholecystitis		1

Table V: DIFFERENCES IN SOME CHARACTERISTICS OF WOMEN WITH ECTOPIC PREGNANCY

	Gynaecological	Surgical
Admissions	67·5%	32·5%
Average blood loss	600 ml	2000 ml
Ruptured	35%	70%
Ectopic pregnancy on right side	54%	70%
Diarrhoea	15%	33%
Incorrect diagnosis preop.	30%	55%

Table VI: PREVIOUS ABDOMINAL SURGERY
(*n* = 226)

Appendicectomy	26 (12%)
Sterilization	21 (9%)
Previous ectopic pregnancy	19 (8%)
Caesarean section	10 (4%)
Ovarian operations	9 (4%)
Other	11 (5%)



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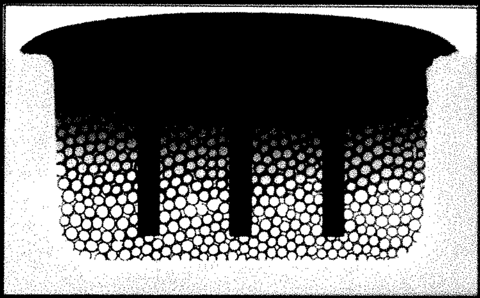

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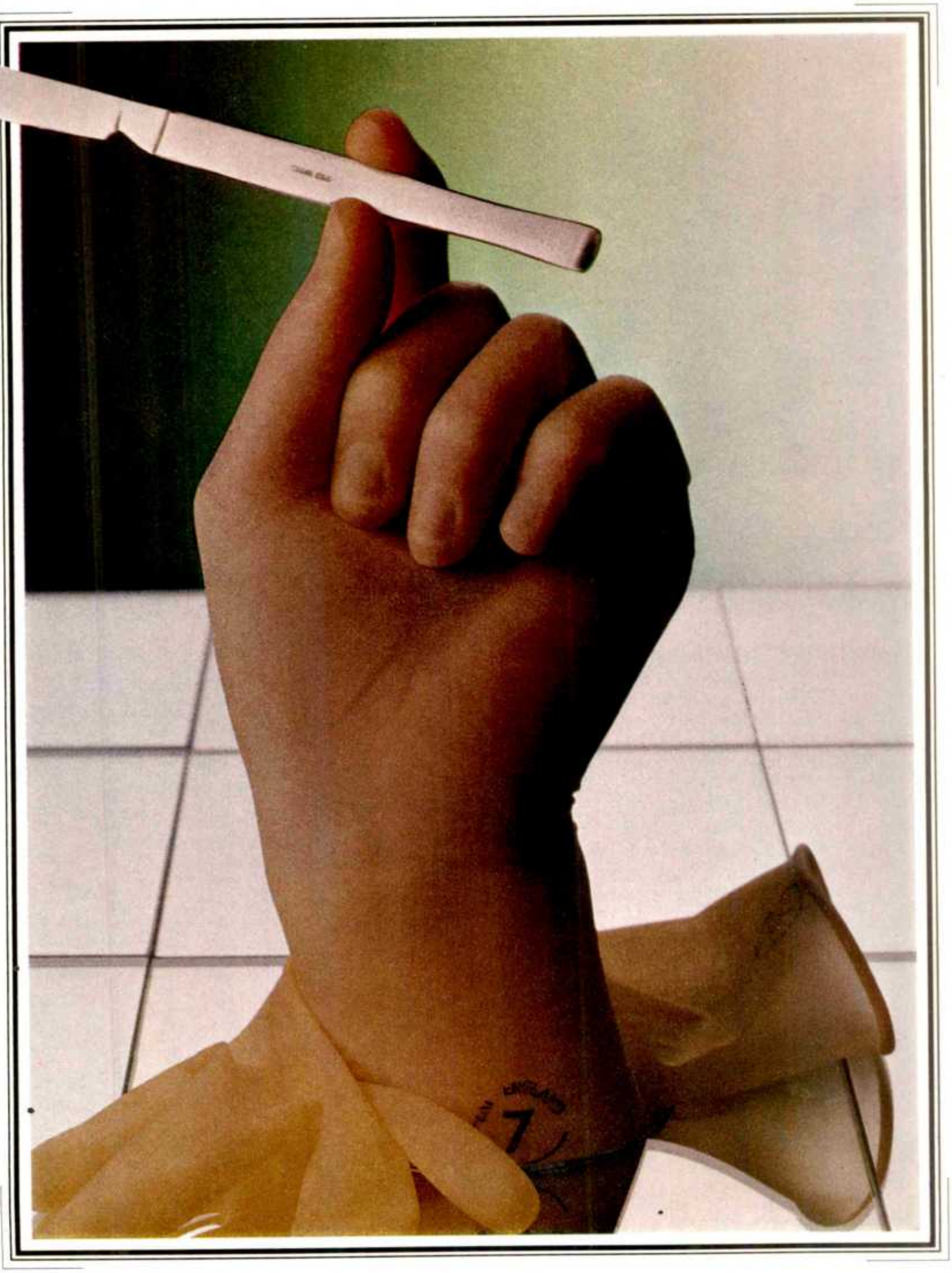

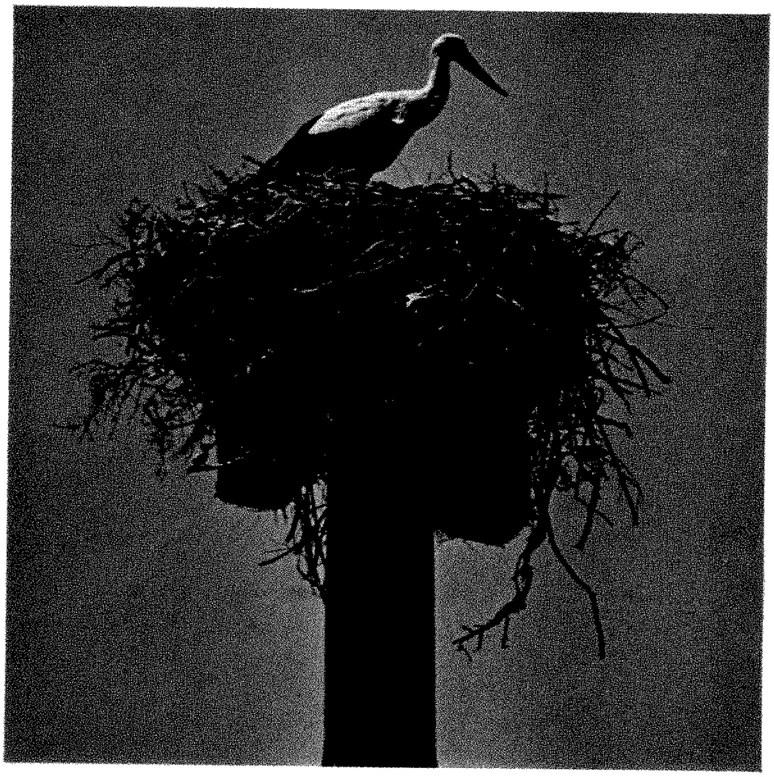

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in 1976–7 only 9 per cent were older than 35 years when admitted with ectopic pregnancy.

Only 30 per cent of the primigravid patients were unmarried, compared with the total population, where 50 per cent of all first pregnancies in Aberdeen are conceived out of wedlock. Ten per cent of parous women were unmarried, widowed or divorced.

Past history

Pelvic sepsis: Ten per cent of patients had a history of pelvic inflammatory disease. This is probably a falsely low figure and many women may have had mild disease without being aware of it or were unwilling to confess to venereal disease. Five patients had a history of pelvic tuberculosis.

Previous abdominal operations: Forty-two per cent of all patients had previously undergone some form of abdominal surgery (*Table VI*). There is a high incidence of peritubular adhesions following any abdominal operation, and at the time of surgery for the ectopic pregnancy 25 per cent of all our cases were documented as having pelvic adhesions.

Intrauterine contraceptive device: The overall incidence of IUCD usage in the series was 7 per cent, and in more recent years the incidence rose to 13 per cent. The IUCD was *in situ* when the ectopic pregnancy occurred.

Fertility investigations: Twenty per cent of patients had had fertility investigations under general anaesthesia.

Parity: About 40 per cent of patients had no children who had lived and 25 per cent were primigravid women. Ectopic pregnancy is usually a disease of low parity except in developing countries.

Symptoms

Symptoms commonly recorded are shown in *Table VII*.

Because many patients complain of intermittent vaginal bleeding they are often referred for investigation of dysfunctional uterine haemorrhage. Lower abdominal pain was almost universal and most patients had some form of bleeding. If the patient has no pain at all and no bleeding the diagnosis is unlikely to be ectopic pregnancy.

Other common symptoms were diarrhoea, fainting attacks and dyspareunia.

Table VII: SYMPTOMS

Vaginal bleeding	
Intermittent	50%
Continuous since LMP	20%
Brown discharge only	20%
No bleeding	10%
Abdominal pain	
Sudden onset, severe	47%
Gradual onset, mild	50%
Suprapubic	37%
Right iliac fossa	22%
Left iliac fossa	18%
Generalized	12%
No pain at all	2%

Signs

The most reliable sign is that of cervical excitation (extreme tenderness when the cervix is moved), and this was found in 85 per cent of the patients who had vaginal examinations. Rebound tenderness was also commonly elicited. A pelvic mass was noted in 45 per cent of cases but in many of these the ectopic pregnancy was found to be on the opposite side to that of the supposed mass. Preoperatively the hunt for a pelvic mass is usually unhelpful as well as being potentially dangerous.

Investigations

There is no preoperative test that will definitely identify an ectopic pregnancy. However, a pregnancy test can be useful if it is positive. This was performed in hospital in 40 per cent of cases and found to be negative in one-third of those patients who had ectopic pregnancy. Sometimes a test done earlier by a general practitioner had been positive but had become negative by the time the patient entered hospital. This was particularly useful information.

Haemoglobin: This was estimated on almost every patient but is of little use in the presence of acute bleeding. However, a falling haemoglobin may indicate the presence of chronic bleeding and haematocele.

White cell count and ESR can be useful in identifying pelvic sepsis.

Ultrasound: This has been used in very few of our patients to diagnose ectopic pregnancy, and even when it has been used it has been most unhelpful. Other units have found it a useful diagnostic aid.

Proof puncture: Needle aspiration of the posterior fornix was performed in 17 per cent of our cases but has been used much less in recent years (*Fig.* 3).

Laparoscopy: There has been a marked increase in the use of laparoscopy to diagnose pelvic pain, and 40 per cent of all ectopics in the series had had a laparoscopy just before laparotomy. This investigation is not generally used on those patients admitted to surgical wards and is not used in shocked patients. There has been a decrease in the number of ruptured ectopics over the years which has been coincident with the increased usage of the laparoscope as a diagnostic tool (*Fig.* 4). It would appear that ectopic pregnancy is being diagnosed at an earlier stage.

Laparotomy: Fifty per cent of our patients were diagnosed by laparotomy to have ectopic pregnancy.

Discussion

The diagnosis of ectopic pregnancy is one of the most difficult and important diagnoses in gynaecology. The difficulty is greatest at general practitioner level where the screening of the 'at risk' patient occurs. There is particular difficulty when the symptoms are minimal and mimic many other less dangerous conditions.

Preoperatively there are no other investigations that definitely point to the diagnosis of ectopic pregnancy, so we are dependent on past history and presentation to identify the 'at risk' group of women. The mean age of women with ectopic pregnancy is decreasing and there was a surprising number of teenage girls in our series. This may be due to the fact that more young girls are having intrauterine contraceptive devices inserted as a means of contraception. Most series report the condition in the older age group, except a series from Zambia in which 70 per cent were under the age of 30 (Lucas and Hassim, 1970).

There is a well-established relationship between pelvic sepsis and ectopic pregnancy. In another large series 20–40 per cent had a history of salpingitis and 50 per cent had microscopic evidence of acute or chronic salpingitis at the time of operation (Jarko, 1949; Douglas, 1963). It was surprising in our study, however, that there was not an increasing association between pelvic sepsis and ectopic pregnancy at a time when the incidence of venereal disease is increasing in this community.

Our incidence of 8 per cent of women who had had a previous ectopic pregnancy, although similar to the Jamaican series (Douglas, 1963), is higher than most series. In 10 series with a total of 1300 ectopic pregnancies there was a 5 per cent incidence of previous ectopic pregnancy (Jarko, 1949).

Failed sterilization is becoming an increasing cause of ectopic pregnancy. An analysis of 77 failed sterilizations showed an incidence of ectopic pregnancy of 16 per cent (Hughes, 1977). Our incidence (7 per cent) of women using an intrauterine contraceptive device compares with other series (Lehfeldt et al., 1970), and it is thought that in Britain the recent increase in ectopic pregnancies could be associated with the general increase in the use of intrauterine contraceptive devices (Beral, 1975).

Many of our patients had had investigations for infertility and others had waited many years between pregnancies or before their first pregnancy before having this ectopic. There is a distinctive group of women who have very poor fertility characteristics, and these women have a high risk of an ectopic pregnancy if they become pregnant at all. It has been estimated that patients having infertility investigations have an eightfold increase in the risk of ectopic pregnancy (Wyper, 1962).

The vast majority of our patients gave a history of bleeding or brown discharge. This is not a universal finding and in another series 20–50 per cent of patients did not give a history of any abnormal bleeding or discharge (Lucas and Hassim, 1970) and 50 per cent of patients did not suspect pregnancy (Hallett, 1975). Lower abdominal pain was almost universal in our series. No pain at all in the history is common (ranging from 10 to 20 per cent of patients) in other reported series.

The commonest sign found was cervical excitation and this is in accordance with other series. It does not, however, distinguish between ectopic pregnancy, pelvic sepsis or other pelvic peritonitis.

Proof puncture as a diagnostic tool has little place in the diagnosis of ectopic pregnancy in centres where laparoscopic examination is easily available. Laparotomy alone was performed in all shocked cases and in the vast majority of women admitted to surgical wards. However, in gynaecological wards, diagnostic laparoscopy was almost universal if the diagnosis of ectopic pregnancy was in doubt. With the aid of the laparoscope we are diagnosing ectopic pregnancies earlier now, before they rupture, and only rarely are patients sent home before the diagnosis is made.

The diagnosis of doubtful cases of ectopic pregnancy has been shown to be difficult at all levels of medical practice. The efficiency of diagnosis can be improved if attempts are made to identify high risk groups of patients from their past history, and if laparoscopic examination is freely used in doubtful cases.

Acknowledgements

I am grateful to Dr George P. Milne for encouraging me to undertake this study and to Professor MacGillivray and consultants at Aberdeen Maternity Hospital for their help. I am also grateful to Ms M. Grassick for her usual superb assistance.

References

BERAL V. (1975) An epidemiological study of recent trends in ectopic pregnancy. *Br. J. Obstet. Gynaecol.* **82**, 775–782.

DHSS (1972) *Report on Confidential Enquiries into Maternal Deaths in England and Wales.* London, HMSO, pp. 82–85.

DOUGLAS C. P. (1963) Tubal ectopic pregnancy. *Br. Med. J.* **2**, 838–841.

HALLETT S. (1975) Repeat ectopic pregnancy. *Am. J. Obstet. Gynecol.* **122**, 520–523.

HUGHES G. J. (1977) Sterilisation failure. *Br. Med. J.* **2**, 1337–1340.

JARKO J. (1949) Ectopic pregnancy. *Am. J. Surg.* **77**, 273–313.

LEHFELDT H., TIETZE C. and GORSTEIN F. (1970) Ovarian pregnancy and the intra-uterine device. *Am. J. Obstet. Gynecol.* **108**, 1005–1009.

LUCAS C. and HASSIM A. M. (1970) Place of culdocentesis in the diagnosis of ectopic pregnancy. *Br. Med. J.* **1**, 200–202.

WYPER J. F. B. (1962) Pregnancy after primary infertility investigation. *Br. Med. J.* **1**, 273–276.

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The effect of uraemia upon wound healing: an experimental study*

J. F. COLIN, P. ELLIOT AND H. ELLIS†

SUMMARY

Acute uraemia was induced in rats by performing a 70 per cent nephrectomy. Uraemia was shown to delay the healing of intestinal anastomoses and abdominal wounds in rats as judged by bursting strength tests. Cellular proliferation was depressed at wound edges but there was no reduction in the total amount of hydroxyproline present in the wounds. Fibroblast growth in tissue culture was affected by the addition both of uraemic plasma and of urea solution to the culture medium. The possible causes of these effects are discussed.

ACUTE renal failure following severe battle injury was noted during World War I (Minami, 1923), but it was not until the Korean War that surgeons suggested that renal dysfunction may impair wound healing (Balch et al., 1955; Teschan et al., 1955; Bluemle et al., 1959). Some experimental evidence (Nayman, 1966; Mott and Ellis, 1967; McDermott et al., 1968, 1971a, b) has shown that certain aspects of wound healing may be adversely affected by uraemia.

The present study investigates the effect of acute uraemia upon the healing of abdominal incisions and anastomoses of the small intestine in the rat. In addition, some observations are made on the growth of rat skin fibroblasts in media containing uraemic plasma and in media containing urea solution.

Material and methods

Production of a uraemia model

Female Sprague Dawley rats weighing between 250 and 300 g were rendered uraemic by performing a 70 per cent nephrectomy. Under intraperitoneal nembutal anaesthesia, the abdomen was opened and the right kidney removed. The left kidney was separated from its surrounding tissues (leaving it attached medially only by the vascular pedicle and the ureter) and the upper and lower thirds of the kidney were removed using a diathermy needle. Blood was taken on alternate days for estimation of the plasma urea and electrolytes and total protein.

Bursting strength of the abdominal wall

A 5-cm-long midline abdominal incision was made. In the control group of rats a right nephrectomy was then performed; in the uraemic group the animals were made uraemic as described above. The abdominal incision was then closed in a standard fashion, using nine interrupted thread sutures. The rats were killed with ether on the third, fifth or seventh postoperative days and the bursting strength of the abdominal wall measured by a technique previously described from this laboratory (De Hann et al., 1974). This comprised the insertion of a rubber condom into the peritoneal cavity through a defect made in the apex of the vagina. The condom was slowly inflated with oxygen from a cylinder at the rate of 100 ml/min and the point at which the wound dehisced was measured on a mercury manometer. The sutures were removed before this procedure was carried out.

Bursting strength of anastomosis of the small intestine

The ileum was transected 10 cm from the caecum and anastomosed end to end with a continuous everting suture of 6/0 catgut. The rats were killed on the third, fifth or seventh postoperative days. The segment of bowel containing the anastomosis was removed together with any adjacent adherent viscera. One end of the segment of bowel was tied with a piece of thread, the segment immersed in normal saline and the bowel inflated with air from a continuous slow injection pump at the rate of 1·5 ml/min. The bursting pressure was that point at which bubbles of air first left the bowel and were recorded on a mercury manometer.

Hydroxyproline estimations

The hydroxyproline content of tissues was estimated by a modification of the method of Woessner (1961). Using this method the hydroxyproline content of normal rat midline abdominal skin and the hydroxyproline content of standard segments of the midline incision in the control and uraemic rats on the third, fifth and seventh postoperative days were estimated. Similarly, the hydroxyproline content of normal small intestine in control rats and normal small intestine in uraemic rats together with the hydroxyproline content of anastomoses of the small intestine on the third, fifth and seventh days in control and uraemic rats was estimated.

Autoradiographic study of healing abdominal skin wounds

Seven rats, 3 uraemic and 4 controls, were used. Five days after a midline abdominal incision had been sutured the rats were given an intraperitoneal injection of tritiated thymidine, 2 μCi/g of body weight, and were killed with ether 60 min later. A segment of the skin wound from the centre of the incision was removed, fixed in 10 per cent formalin and sections were cut and stained with haematoxylin and eosin. Autoradiographs were prepared by the dipping technique using Ilford Nuclear Research emulsion G5. These were exposed for 3 weeks and subsequently examined under the light microscope. The percentage of labelled fibroblasts and capillary endothelioid cells in the granulation tissue under the epidermis provided an estimate of cellular proliferation. The criterion for labelling was 8 grains/nucleus, which was well above the background grain density.

Using a graticule, all the cells in three fields on either side of the incision, at the wound edge, were counted. Thus six fields were counted in each wound and a minimum of 700 cells were counted in each specimen. The labelling index is the percentage of cells that are labelled in each specimen. Although labelled cells could be seen in the basal cells of the epidermis and in the hair follicles, these were never counted. Neither was any consideration given to the phase of the skin cycle of the adjacent skin.

Fibroblast culture in uraemic rat plasma and urea solution

Small pieces of abdominal skin were removed from female Sprague Dawley rats, stripped of all fat and hair, cut into pieces of approximately 1 mm square and placed in tissue culture Petri dishes. Cover slips were placed on top of the pieces of skin in order to keep them flat on the surface of the Petri dishes and medium TC 199 (Hepes buffer) with heat-inactivated 20 per cent fetal bovine serum (FBS) was added. The Petri dishes were incubated for 5 days at 37 °C until outgrowths of fibroblasts were seen. The fibroblasts were subsequently seeded into Falcon bottles where they were allowed to grow. Viable fibroblasts were taken from the Falcon bottles and seeded in known numbers into Teflon rings which contained medium TC 199 20 per cent FBS, or medium TC 199 20 per cent FBS plus uraemic plasma (urea 66 mmol/l), or medium TC 199 20 per cent FBS plus pure urea solution (66 mmol/l). After 48 h the fibroblasts were examined under the light microscope and the condition and the shape of the cells and the type of cell growth recorded.

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* This work is the basis for a London University MS thesis.

† Surgical Unit, Westminster Hospital, London SW1.

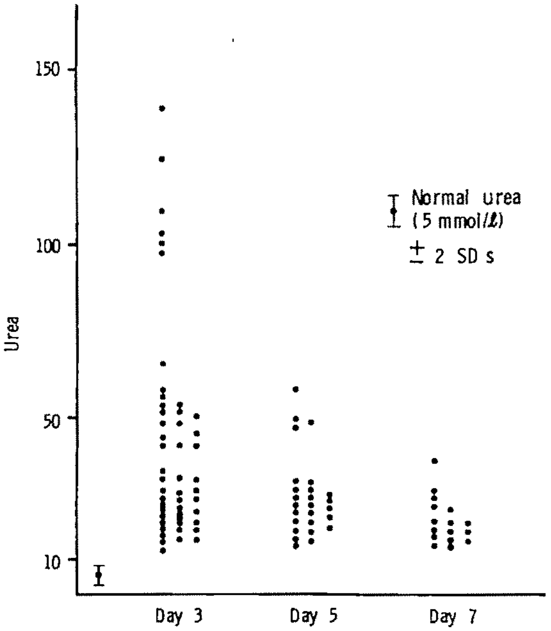
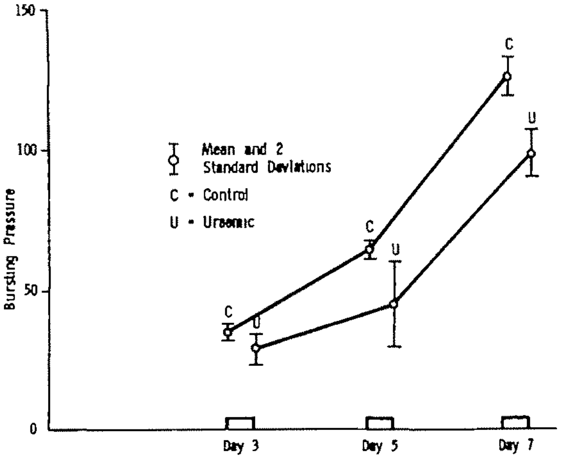


Fig. 1. Blood urea levels (mmol/l) on days 3, 5 and 7 following 70 per cent nephrectomy.

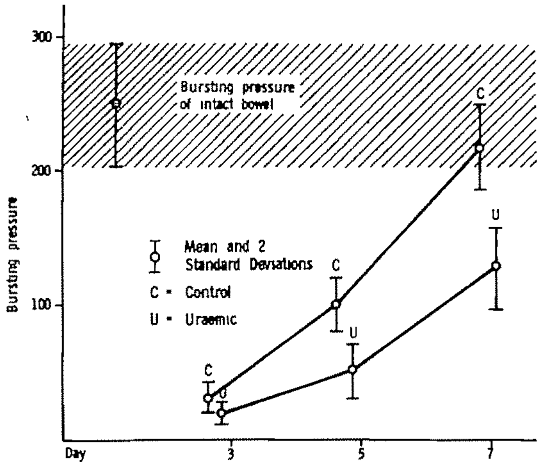


Mean	35 8	28 6	64 8	46 8	126 0	90 4
S.D.	3 2	7 8	3 0	16 5	7 0	8 5

Fig. 2. Bursting pressures (mmHg) of 5-cm-long midline abdominal wounds in control and uraemic rats.

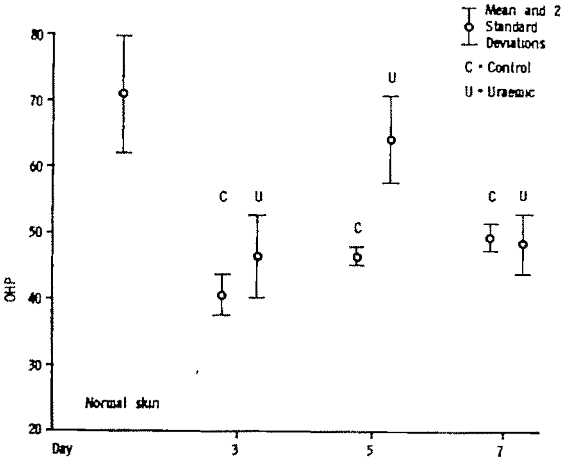
In a second group of experiments, microsyringes were used to seed 6000 fibroblasts of approximately 99 per cent viability into the microcytotoxicity plates. One group of microcytotoxicity plates contained fibroblasts in medium TC 199 plus 20 per cent FBS only. In a second group the fibroblasts were cultured in the same medium plus additional uraemic plasma. The plasma contained differing amounts of urea, namely 66 mmol/l, 22 mmol/l, 15 mmol/l and 8 mmol/l. In a third group fibroblasts were grown in medium TC 199 20 per cent FBS plus pure urea solution. Again the urea solution contained different amounts of urea, namely 66 mmol/l, 22 mmol/l, 15 mmol/l and 8 mmol/l respectively.

The plates were incubated for 24 h after which they were examined for general growth, numbers and shape, using phase contrast microscopy.



Mean	247	33	20	99	53	212	135
S D.	47 3	14	7	22	26	40	29

Fig. 3. Bursting pressures (mmHg) of small intestine anastomoses in control and uraemic rats 3, 5 and 7 days after the anastomosis.



Mean	71 13	41 10	47·68	46 36	64 72	49 32	47 64
S.D	9 26	6 95	14 53	2 50	13 43	5 34	10 88

Fig. 4. Hydroxyproline content (mg/g dry tissue) of abdominal skin wounds on days 3, 5 and 7 in control and uraemic rats.

Results

The method used to produce uraemia caused a significant ($P<0.00001$) elevation of the blood urea level which lasted over a period of 7 days. The mortality was 10 per cent (*Fig.* 1).

The observed levels of blood urea in both the control and uraemic rats were not normally distributed (Kolmogorov–Smirnov test for goodness of fit: Kolmogorov, 1941; Smirnov, 1948). For this reason the Mann–Whitney (1947) test was used to analyse the data. As there was an *a priori* assumption that the bursting strength in uraemic rats was less than in controls, one-tailed probability values are given in the results. The null hypothesis was that there was no significant difference between controls and uraemics. A significant difference was defined as $P<0.01$.

Table I: BURSTING STRENGTH

	Uraemic group			Control group		
Day	No. of animals	BS (mmHg±s.d.)	Median BS	No. of animals	BS (mmHg±s.d.)	Median BS
Abdominal incisions						
3	8	28·6 (±7·8)	24·5	10	35·8 (±3·2)	35·5
5	8	46·8 (±16·5)	44	10	64·8 (±3 0)	64·5
7	8	90·4 (±8·5)	86·5	10	126·0 (±7 0)	127·5
Anastomoses						
3	10	20 (±7·0)	18·5	9	33 (±14)	29
5	8	53 (±26)	45	8	99 (±22)	98
7	8	135 (±29)	137	9	212 (±40)	200

BS, Bursting strength.

Table II: HYDROXYPROLINE CONTENT

	Uraemic group			Control group		
Day	No. of animals	Mean OHP (mg/g±s.d.)	Median OHP (mg/g)	No. of animals	Mean OHP (mg/g±s.d.)	Median OHP (mg/g)
Abdominal incisions						
3	3	47·7 (±14·5)	41·6	3	41·1 (±6·9)	40·1
5	7	64·7 (±13·4)	63·4	5	46·6 (±2·5)	46·2
7	5	47·6 (±10·9)	47·6	5	49·3 (±5·3)	52·1
Anastomoses						
3	6	8·1 (±2·3)	8·7	5	6·8 (±1·4)	6·7
5	6	12·7 (±5·3)	12·2	7	11·0 (±3·3)	10·4
7	5	13·8 (±5·3)	10·8	8	11·4 (±2·7)	10·3

OHP, Hydroxyproline.

Table III: CELL COUNTS IN SKIN WOUNDS OF RATS ON FIFTH POSTOPERATIVE DAY

No. of cells in 6 fields	No. of labelled cells	Labelling index	Urea (mmol/l)
810	38	3·5	42
791	25	3·2	31
1105	83	7·5	17
940	78	8·3	9
1003	110	10·7	9
929	129	13·9	7
1390	150	10·8	4

Tests of bursting strength

Abdominal incisions: The bursting strength in the control animals was significantly higher than that in the uraemic animals on the third, fifth and seventh postoperative days ($P = 0{\cdot}01$ 3 days, $P < 0{\cdot}01$ 5 days, $P < 0{\cdot}0005$ 7 days) (*Table I, Fig.* 2).

Intestinal anastomoses: The bursting strength of normal small intestine was the same in control and uraemic animals (*Table I, Fig.* 3).

The bursting strength of anastomoses of the small intestine was greater in control rats than in uraemic rats on the third, fifth and seventh postoperative days ($P < 0{\cdot}025$ 3 days, $P < 0{\cdot}0025$ 5 days, $P < 0{\cdot}001$ 7 days).

Hydroxyproline measurements

Skin wounds: There was no difference in the amount of hydroxyproline present in the abdominal skin wound in the control or uraemic rats on the third and seventh postoperative days (*Table II, Fig.* 4). On the fifth postoperative day the uraemic group contained more hydroxyproline than the control group ($P < 0{\cdot}0045$).

Intestinal anastomoses: Unwounded small bowel of control and uraemic rats contained the same amount of hydroxyproline (*Table II, Fig.* 5).

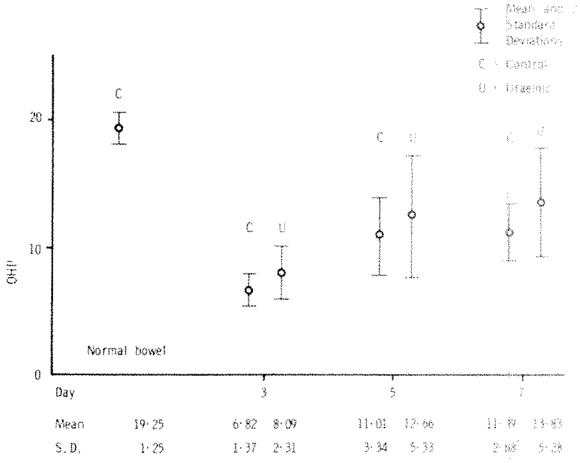


Fig. 5. Hydroxyproline content (mg/g dry tissue) of small bowel anastomoses on days 3, 5 and 7 in control and uraemic rats.

There was no difference between the amount of hydroxyproline present in the anastomoses of the small intestine in the control and uraemic group on the third, fifth and seventh postoperative days. In addition, a non-parametric regression of hydroxyproline levels, in both skin wounds and anastomoses, against blood urea levels showed no association ($r = -0{\cdot}07$).

Autoradiographic study (*Table III*)

The granulation tissue of the wounds in the control and uraemic groups contained labelled fibroblasts, endothelioid cells and mononuclear cells. However, the number of labelled cells was fewer in the uraemic

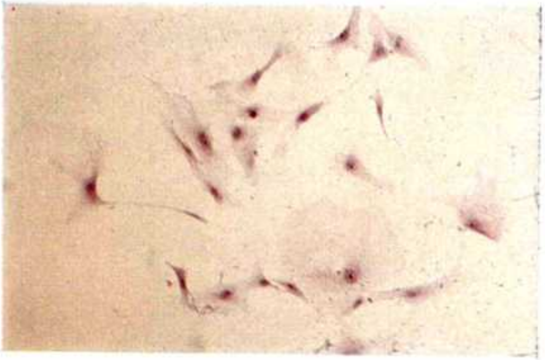


Fig. 6. Normal fibroblasts grown in culture. (× 800.)

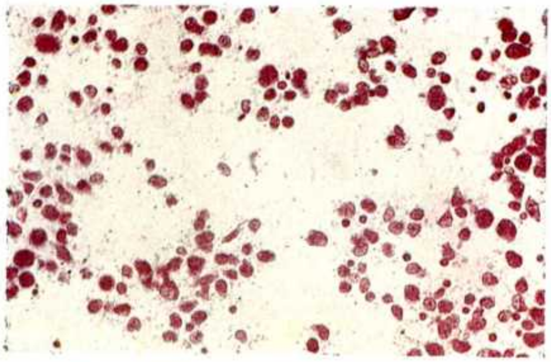


Fig. 7. Abnormal fibroblasts grown in culture to which uraemic plasma has been added. (× 800.)

group than in the controls. In one specimen with a blood urea level of 7 mmol/l, the labelling index was 13·9 per cent whilst in another specimen in which the blood urea was 31 mmol/l the labelling index was only 3·2 per cent.

Fibroblast culture

Fibroblasts grown from rat skin in culture medium TC 199 20 per cent FBS grew well, were typical in appearance and the viability of the cells was good (*Fig.* 6). When uraemic plasma was added to the medium, the subsequent behaviour of fibroblasts varied with the amount of urea in the plasma. In media containing urea 22 mmol/l or 66 mmol/l, although the cells were viable, they were all rounded in appearance and did not grow profusely (*Fig.* 7). If the media contained plasma with 15 mmol/l urea, most of the fibroblasts were normal in shape, though some were rounded, but they were all viable. In the media containing plasma with 8 mmol/l urea the growth of fibroblasts was normal, their shape and number were normal and the viability of the cells was good.

The addition of pure urea solution had a profound, and much more marked, effect on the growth of fibroblasts. When urea 66 mol/l was added to the medium, many (average 61 per cent) of the cells died and the remainder were rounded in appearance. With the addition of urea 22 mmol/l to the media, about half (average 46 per cent) of the cells died and the remainder were rounded in shape. If the media contained urea 5 mmol/l most of the cells were alive but rounded in shape and the growth only half as good as in the normal media without the addition of urea solution. In media containing urea solution 8 mmol/l, some of the cells were typical fibroblasts, although most were rounded in appearance. The viability of the cells was good, however, although the growth was only two-thirds of normal.

Discussion

Our studies have shown that acute uraemia in the rat is associated with a lowering of the bursting pressure of midline abdominal incisions and of anastomoses of the small intestine up to the seventh postoperative day. In addition, we have shown that there is a decreased rate of cellular proliferation at the healing wound edge, but no reduction in the total amount of hydroxyproline present in the wound. Our tissue culture studies have shown that fibroblasts grown in media containing uraemic plasma do not have a normal form. However, the effect of the addition of uraemic plasma is not so deleterious as is the addition of equivalent amounts of pure urea solution.

Changes in the concentration of salts and amino acids in a tissue culture medium can result in morphological changes in the cultured cells. However, growth inhibition and killing of cells are not observed (Paul, 1970), but these did occur with the addition of urea or uraemic plasma to the tissue culture medium.

A depressed rate of granulation tissue formation in healing wounds in uraemic mice has previously been reported (McDermott et al., 1968) and epithelial cell division in the mouse jejunum, oesophagus and stomach has also been shown to be depressed in uraemia (McDermott et al., 1971a, b; Castrup et al., 1972). It has also been shown that the healing of peritoneal defects in uraemic rabbits is delayed and collagen fibre formation, in the depth of the defects, lags behind that of controls (Mott and Ellis, 1967). Uraemic serum has been shown to have cytotoxic effects in other spheres (Arpels and Southam, 1969; McDermott, 1971), and acute renal failure has been shown to have an inhibitory effect on cell division in lymphoid tissue (Burwell et al., 1962; Silk, 1967).

Our studies on the total hydroxyproline content of the healing wounds showed that there was no difference between the controls and the uraemic rats except in one instance. This was on the fifth postoperative day at which time the hydroxyproline content of the abdominal skin wound was found to be higher in the uraemic group than in the control group. Clearly, the decrease in the bursting strength of the abdominal incisions and the anastomoses in the uraemic rats was not accompanied by a decrease in the total hydroxyproline content of the wound. However, the method used for harvesting the tissues for hydroxyproline estimation in this study could have resulted in small differences in the hydroxyproline values not being recorded. The estimation of the total hydroxyproline content of the healing wound does not differentiate between the new collagen that has been formed and the old collagen that has been broken down. The decrease in the bursting strength in the uraemic group without a change in hydroxyproline content could be explained by the production of a collagen of poor quality, as occurs in lathyrism, or by an increased destruction of old collagen, affecting the strength of the wound without changing the total hydroxyproline content. Clearly further studies using tritiated proline as an isotope label to determine the rate of new collagen production

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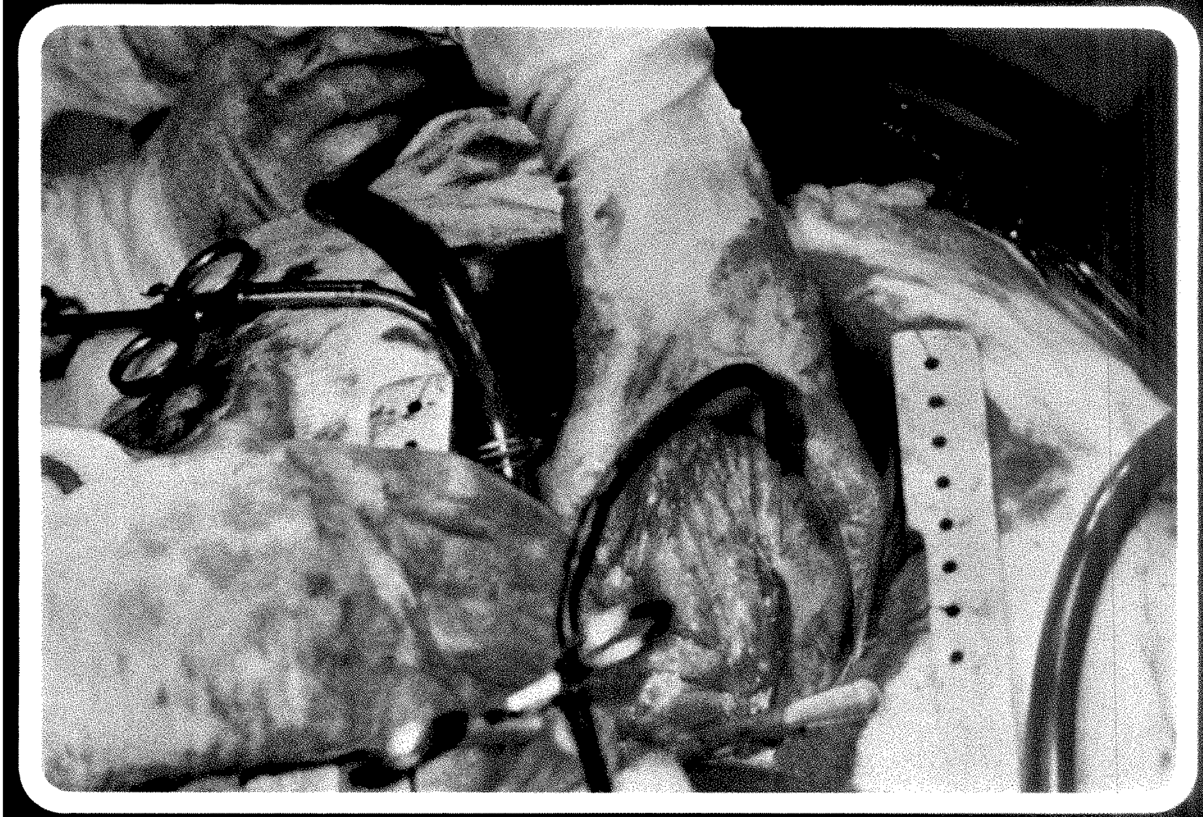

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1 Brit med J (1978), **1**, 1603
2 Thorax (1978), 33, **1**, 130
3 Brit med J (1978), **2**, 536
4 Brit med J (1970), **4**, 455
5 Zbl Bakt Hyg I Abt Orig A (1976), **236**, 235

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Ampoules of 200,000 KIU*
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PL0010/5900

1) Schneider et al., Chirurg **47,** 185 (1976)
2) McMichan et al., Med. Welt **27,** 2331 (1976)

(Cronin et al., 1968; Madden and Smith, 1970) would be of interest.

In uraemia enzyme systems, biochemical pathways and cellular metabolism are altered (Hollunger, 1955; Galloway and Morgan, 1964). The levels of free and bound hydroxyproline in the plasma are raised in uraemia due to the impairment of the hepatic enzyme, hydroxyproline oxidase (Avioli et al., 1969), so it would not be surprising if the synthesis of new collagen or the degradation of old collagen in healing wounds was altered in uraemia.

Circulatory inhibitors to skin collagenases have been demonstrated in human serum (Eisen et al., 1970) and Hawley and Page Faulk (1970) have identified an alpha-globulin in the sera of rabbits which inhibits the action of collagenase from the rabbit colon. Following injury the amount of circulatory inhibitor decreases. Alterations in the fractions of the plasma proteins in uraemia are known to occur. Amino acid metabolism and protein synthesis are altered (Shear, 1969) and antibody production is decreased (Souhami, 1971). In humans with uraemia increased levels of an alpha-2-globulin have been found in the serum (Finkle et al., 1956). It could be that in uraemia there are alterations in the amount of circulatory collagenase inhibitors, so that lysis exceeds synthesis, thus lowering the strength of wounds.

Protein deficiency or anaemia was not responsible for the observed changes in the bursting strengths in the uraemic group as there were no changes in these factors when compared with the controls. Although the uraemic rats may have been dehydrated, there were no changes in the plasma sodium levels when compared with the controls, so this is unlikely to have been an important factor. The uraemic rats all lost more weight than the controls so that by the seventh day they had lost on average 10 per cent of their initial body weight. However, Irvin and Hunt (1974) showed that malnutrition impaired colonic healing in rats only if over 34 per cent of the body weight had been lost.

This study has clearly shown that acute uraemia in rats delays the early phase of wound healing and severely affects cellular proliferation in the wound and fibroblast growth in tissue culture media. The most likely explanation is that the uraemic state causes this effect by altering some processes of cellular metabolism.

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References

ARPELS C. and SOUTHAM C. M. (1969) Cytotoxicity of sera from healthy patients and patients with cancer. *Int. J. Cancer* **4**, 548–559.

AVIOLI L., SCHARP C. and BIRGE S. (1969) Catabolism of free hydroxyproline in chronic uraemia. *Am. J. Physiol.* **217**, 536–540.

BALCH H. M., MERONEY W. H. and SAKO Y. (1955) Observations on the surgical care of patients with post-traumatic renal insufficiency. *Surg. Gynecol. Obstet.* **100**, 439–452.

BLUEMLE L. W., WEBSTER G. D. and ELKINTON J. R. (1959) Acute tubular necrosis. *Arch. Intern. Med.* **104**, 180–197.

BURWELL R. G., SMIDDY F. G. and PARSONS F. M. (1962) The effects of uraemia upon the survival of skin homografts. *Br. J. Surg.* **49**, 558–568.

CASTRUP H. J., LENNARTZ K. J. and PEIPER H. J. (1972) The effect of uraemia on the epithelial regeneration of the stomach and intestine. *Arch. Fr. Mal. App. Dig.* **61**, 309c.

CRONIN K., JACKSON D. S. and DUNPHY J. E. (1968) Specific activity of hydroxyproline-tritium in the healing colon. *Surg. Gynecol. Obstet.* **126**, 1061–1065.

EISEN A. Z., BLOCK K. and SAKAI T. (1970) Inhibition of human skin collagenase by human serum. *J. Lab. Clin. Med.* **75**, 258–263.

FINKLE A. L., PARISH J. F., KANG S. J. et al. (1956) Serum protein alterations in uraemia. *N. Engl. J. Med.* **254**, 1203–1210.

GALLOWAY R. E. and MORGAN J. M. (1964) Serum pyruvate and lactate in uraemia. *Metabolism* **13**, 818–822.

DE HAAN B., ELLIS H. and WILKS M. (1974) The role of infection in wound healing. *Surg. Gynecol. Obstet.* **138**, 693–700.

HAWLEY P. R. and PAGE FAULK W. (1970) A circulatory collagenase inhibitor. *Br. J. Surg.* **57**, 900–904.

HOLLUNGER G. (1955) Guanidine and oxidative phosphorylation. *Acta Pharmacol. Toxicol.* Suppl. 1, p. 84.

IRVIN T. T. and HUNT T. K. (1974) Effect of malnutrition on colonic healing. *Ann. Surg.* **180**, 765–772.

KOLMOGOROV A. (1941) Confidence limits for an unknown distribution function. *Ann. Math. Statist.* **12**, 461–468.

MADDEN J. W. and SMITH H. C. (1970) The rate of collagen synthesis and deposition in dehisced and resutured wounds. *Surg. Gynecol. Obstet.* **130**, 487–493.

MARKSON J. L. and RENNIE J. B. (1956) The anaemia of chronic renal insufficiency. *Scot. Med. J.* **1**, 320–322.

MCDERMOTT F. T. (1971) The effect of a 10 per cent human uraemic serum upon human fibroblasts in cell cultures. *J. Surg. Res.* **11**, 119–123.

MCDERMOTT F. T., NAYMAN J. and DE BOER W. G. (1968) Effect of acute renal failure on wound healing. Histology and autoradiography in the mouse. *Ann. Surg.* **168**, 142–146.

MCDERMOTT F. T., NAYMAN J. and DE BOER W. G. (1971a) Epithelial cell division in acute renal failure. A radioautographic study in the oesophagus of the mouse. *Br. J. Surg.* **58**, 52–55.

MCDERMOTT F. T., NAYMAN J. and DE BOER W. G. (1971b) Effect of acute renal failure upon cell division in the jejunum. *Ann. Surg.* **174**, 274–282.

MINAMI S. (1923) Kidney damage after burial. *Virch. Arch.* **245**, 247–267.

MOTT T. J. and ELLIS H. (1967) A method of producing experimental uraemia in the rabbit with some observations of the influence of uraemia on wound healing. *Br. J. Urol.* **39**, 341–345.

NAYMAN J. (1966) Effect of renal failure upon wound healing in dogs. *Ann. Surg.* **164**, 227–235.

PAUL J. (1970) In: *Cell and Tissue Culture*, 4th ed. Edinburgh, Livingstone.

SHEAR L. (1969) Internal redistribution of tissue protein synthesis in uremia. *J. Clin. Invest.* **48**, 1252–1257.

SILK M. R. (1967) The effect of uraemic plasma on lymphocyte transformation. *Invest. Urol.* **5**, 195–199.

SMIRNOV N. V. (1948) Table for estimating the goodness of fit of empirical distributions. *Ann. Math. Statist.* **19**, 279–281.

SOUHAMI R. L. (1971) Antibody production in uraemic mice. *Clin. Sci.* **40**, 11P.

TESCHAN P. E., POST R. S., SMITH L. H. et al. (1955) Post-traumatic renal insufficiency in military casualties. *Am. J. Med.* **18**, 172–186.

WOESSNER J. F. (1961) The determination of hydroxyproline in tissue and protein samples. *Arch. Biochem. Biophys.* **93**, 440–447.

YENDT E. R., CONNOR T. B. and HOWARD J. E. (1955) *In vitro* calcification of rachitic rat cartilage in normal and pathological human serum with some observations on the pathogenesis of renal rickets. *Bull. Johns Hopkins Hosp.* **96**, 1–19.

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The presentation of gastrointestinal lymphoma: study of a population

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SUMMARY

The clinical presentation and findings in 45 patients with lymphoma of the gastrointestinal tract occurring in an unselected population are described. Nineteen patients presented as emergencies with haemorrhage, perforation, pyloric stenosis or intestinal obstruction. Systemic symptoms, peripheral lymph node enlargement and hepatosplenomegaly were rare, and a preoperative diagnosis of lymphoma was seldom made. Endoscopy was superior to radiology in defining lesions in the stomach and duodenum. Lesions which were multicentric, or of unusual macroscopic appearance, were common in the small bowel, and these should raise the suspicion of lymphoma.

Local and systemic recurrence was common, but was not always fatal. Patients with gastric lymphomas survived longer than those with intestinal disease.

THE organization of medical services in North-East Scotland (Grampian Region) provides a unique opportunity for unselected epidemiological study. The area is well defined, with a population of 475 000, and all patients with major disease are referred to the Aberdeen Teaching Hospitals. In this population a study has been made of both planned and emergency admissions of patients found to have gastrointestinal lymphomas over the 6 years 1972–7. Gastrointestinal lymphoma is considered to be a rare disease in adults in Great Britain, but 45 cases were traced in 6 years, 19 presenting as emergencies. Previous British (Azzopardi and Menzies, 1960; Dawson et al., 1961) and North American (Joseph and Lattes, 1966; Bush and Ash, 1969; Loehr et al., 1969; Hertzer and Hoerr, 1976; Lewin et al., 1978) reviews have come from specialist or referral centres, which may see relatively few emergency cases. The objective of this paper is to show the ways in which this condition presents, and to highlight the difficulties in reaching a definitive diagnosis before and during surgery.

Patients and methods

The Aberdeen Hospitals serve the population of the Grampian Area, and inhabitants of the Orkney and Shetland Islands with major disease also come to Aberdeen. The records of patients from these areas with proved gastrointestinal lymphoma were obtained. The files of the Department of Pathology, University of Aberdeen (which examines biopsy material from the whole area), and of the Information Unit of the Grampian Area Health Board have also been searched.

A total of 291 cases of non-Hodgkin's lymphoma was seen during 1972–7; there were 45 patients in whom lymphomatous involvement of the stomach or intestine was the principal site of disease. Mesenteric involvement alone did not justify inclusion. In 40 patients the gastrointestinal tumour was the only clinical evidence of disease. In a further 5 patients coexisting evidence of lymphoma at other sites (in neck nodes, thyroid, testis and chest wall) was present, but involvement of the gastrointestinal tract was clearly the predominant disease in each instance. There was histological confirmation of gastrointestinal involvement in 42 cases. In the other 3 patients, who had histologically proved lymphoma at another site, there was radiological and endoscopic evidence of involvement of the stomach, duodenum and ileum.

Staging was usually carried out postoperatively, according to the Ann Arbor classification (Carbone et al., 1971), and by definition all had extranodal disease denoted by the suffix 'E'. Patients who recovered from surgery and were adequately staged were treated with wide-field abdominal radiotherapy if there was known or probable local residual disease. Patients with localized disease in whom surgical removal was considered complete were, during the earlier period of the study, observed and appropriate treatment with either chemotherapy or radiotherapy begun at any sign of further disease; in the later stages of this series, such patients were treated immediately with adjuvant chemotherapy in view of the high recurrence rate found in earlier patients. Patients with evidence of extra-abdominal disease (most often mediastinal node involvement) were treated with chemotherapy, using cyclophosphamide, doxorubicin, vincristine and prednisolone intermittently, sometimes after abdominal radiotherapy.

The length of survival and the time to first clinical evidence of recurrence were noted.

Results

Table I shows the distribution of the series according to site of tumour, patient's age and clinical stage. There were 25 males and 20 females. Four patients, 2 with gastric and 2 with small bowel disease, were under the age of 30, while half the patients were over the age of 65 at the time of diagnosis. Where multifocal tumours were present, they were in the same organ, except in 2 cases with small bowel lymphoma, where a second tumour was present in the large intestine. Tumours ranged in size from 1·5 to 30 cm in maximum dimension, with a mean of 6 cm. Thirty-eight cases were regarded as stage IE or IIE, only 7 being more generalized. Enlarged mesenteric nodes were seen and biopsied in 21 cases at laparotomy, but found to be histologically involved in only 11, the remainder showing reactive changes. In 2 cases small involved nodes were found by the pathologist.

Nineteen patients (40 per cent) presented as surgical emergencies (*Table II*). Symptoms of weight loss (7 cases) and abdominal pain (7 cases) preceded the acute episode by 1–12 months (mean 4 months) in the patients with gastric lymphoma. In those with small and large bowel tumours, patients presenting with perforation admitted to no prior symptoms, but those with obstruction frequently had had symptoms, often intermittent, for from 1 week to 6 months before hospital admission.

Among the non-emergency patients symptoms suggested abdominal malignant disease (*Table III*). The mean duration of symptoms was 7 months for gastric lesions (range 2–36 months) and 6 months for intestinal lesions (range 2–16 months). The other clinical features are shown in *Table III.*

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Gastric lymphomas

Sixteen of the 22 patients were male. Five had had radiologically proved peptic ulceration in the past (3 duodenal and 2 gastric ulcers) and a further 4 gave a history of typical ulcer pain over periods of more than 5 years. A barium meal was performed in 19 cases, suggesting malignancy in 11, a benign gastric ulcer in 4 and failing to detect any gastric lesion in 4. Endoscopy was performed in 12 patients, and the appearances were suspicious of malignancy in 9. A biopsy was obtained in 11 cases; it confirmed malignancy in 3 cases and suggested lymphoma in 1 of these. In another case, thought to be benign at gastroscopy, histological examination of the biopsy specimen was suggestive of malignancy. Altogether, 14 patients were considered preoperatively to have a malignant gastric ulcer. All 21 patients operated on were recognized by the surgeon to have malignant disease but no lesion was suspected of being a lymphoma, although in 2 patients the appearances were noted to be unusual; one had an ulcer with rolled edges but without the infiltration of a carcinoma, the other showed diffuse plaque-like thickening of the gastric wall.

Small bowel lymphoma: Of the 15 cases, there were 2 proved and 1 possible case of antecedent coeliac disease, while one other patient had evidence of malabsorption. In 8 cases where barium meal and follow-through was performed, mucosal infiltration was suggested in 3, extrinsic jejunal compression noted in 2 and a non-specific abnormality of the terminal ileum in 1. Thirteen patients underwent an operation, 9 as emergencies (6 for perforation with peritonitis, 1 for small bowel obstruction, 1 for a possible twisted ovarian cyst and 1 for appendicular abscess).

The common operative finding was of a length of pale thickened intestine, often associated with considerable mesenteric thickening and lymph node involvement. When perforation had occurred, the opened specimen showed the perforation to be at the centre of a penetrating mucosal ulcer. In 2 cases the mural thickening had produced occlusion of the

Table I: AGE, SITE AND EXTENT OF THE 45 GASTROINTESTINAL LYMPHOMAS AND THEIR DISTRIBUTION BY CLINICOPATHOLOGICAL STAGE

Site	Mean age (range)	No. of cases	Multifocal lesions	Stage IE	IIE	IIIE	IVE
Stomach	56 (30–75)	22	2	11	7	2	2
Small intestine	64 (26–85)	15	5	9	3	2	1
Large intestine	64 (50–75)	8	3	4	4	—	—
Total	60±14*	45	10	24	14	4	3

Clinicopathological staging according to Carbone et al. (1971).
* Standard deviation.

Table II: PRESENTING FEATURES, BY SITE, OF 19 CASES OF GASTROINTESTINAL LYMPHOMA PRESENTING AS EMERGENCIES

Feature	Gastric	Small intestine	Large intestine
GI bleeding	4	—	—
Perforation	1	6	2
Obstruction	2	3	1

Table III: PRESENTING FEATURES, BY SITE, OF 26 CASES OF GASTROINTESTINAL LYMPHOMA PRESENTING AS NON-EMERGENCIES

Feature	Gastric ($n = 15$)	Intestinal ($n = 11$)
Pain	13 (7)	9 (6)
Weight loss	12 (7)	10 (7)
Anorexia or vomiting	9 (7)	6 (6)
Diarrhoea	—	6 (6)
Mass	4	7
GI bleeding	1	2
Malabsorption	—	2
Hepatomegaly	2	2
Splenomegaly	2	2
Lymphadenopathy	—	2

The figures in parentheses represent mean duration in months.

Table IV. CLINICAL DATA ON THE 14 PATIENTS WITH GUT LYMPHOMA WHO DEVELOPED RECURRENCE WITHIN THE OBSERVATION PERIOD

Initial site	Excision (macroscopic)	Initial therapy	Onset to recurrence (mth)	Site of recurrence	Survival after recurrence (mth)
Stomach*	Incomplete	—	27	Liver, bowel	35†
Stomach*	Incomplete	CT	13	Bowel	0
Stomach	Complete	CT	12	Brain	0
Stomach	Complete	—	3	Lungs, bowel, spleen	3
Stomach	Incomplete	—	16	Stomach	2
Stomach	Complete	RT	1	Stomach	3
Small intestine*	Complete	CT	6	Bowel, liver, spleen, nodes	0
Small intestine*	None	CT	13	Bowel	11†
Small intestine*	Incomplete	CT	8	Axilla	7
Small intestine	Complete	—	11	Bowel	36
Small intestine	Incomplete	CT	24	Mediastinum, neck, breast	32
Small intestine	Complete	—	2	Bowel	3
Large intestine	Incomplete	CT	10	Bowel	43†
Large intestine	Complete	—	14	Chest wall	1

CT, Chemotherapy; RT, radiotherapy.
* Multifocal.
† Alive December 1978.

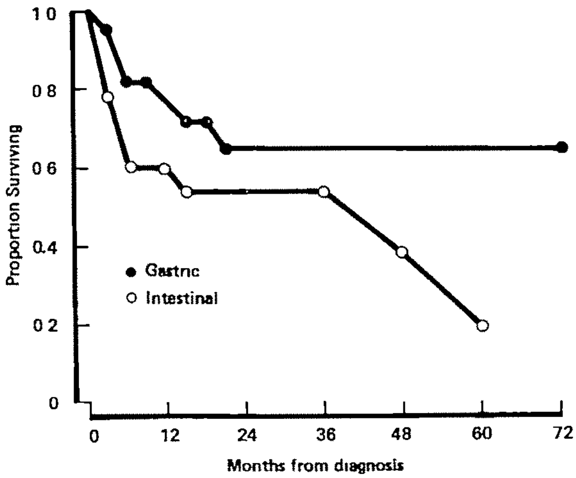

Fig. 1. Life table analysis of survival in 45 cases of gastric and intestinal lymphoma.

lumen and 1 of these patients had a perforation above the obstruction.

Large bowel lymphoma: Of the 8 patients, 2 presented with rectal bleeding, 1 with obstruction and the others with vague abdominal pain, diarrhoea and weight loss. Localized perforations were found in 2 cases. Barium enema examination was performed in 6 cases and the radiologist suggested malignancy in 3 cases of caecal lymphoma and diagnosed malignant stricture in one colonic lymphoma and Crohn's disease in another; the enema failed to demonstrate any abnormality in 1 patient. The findings both at presentation and at operation were indistinguishable from colorectal carcinoma.

Of all 45 cases, the presence of lymphoma was suspected prior to laparotomy in only 7, of whom 5 had coexisting lymphoma at other sites. Gallium-67 scan showed increased abdominal uptake in all 7 patients in whom it was performed. Of the remaining 38 cases, the preoperative diagnosis was suspected malignant tumour in 25.

Operation was performed in 41 patients and removal was regarded as complete in 28 of these. Clinical staging, including scans and bone trephine biopsy, was carried out in all patients fit for further treatment. Eleven patients were treated with wide-field abdominal telecobalt therapy, 6 immediately after operation and 5 later for recurrence. Twenty-two patients had cytotoxic chemotherapy (normally cyclophosphamide, doxorubicin, vincristine and prednisolone), 16 postoperatively and 6 later for recurrence.

There were 14 recurrences, purely local in 7, at a mean of 11 months after diagnosis of the first lesion (*Table IV*). Recurrence was not always fatal and 4 patients were alive more than 30 months later. One patient subsequently developed a perforated duodenal ulcer, another an ileal perforation; both sites were histologically free from tumour and abdominal irradiation had not been given. Nineteen patients have died, 14 within 6 months of diagnosis. Four of these died postoperatively of pulmonary embolism or infection—2 being patients presenting with perforation. Two patients suffered fatal septicaemia while having chemotherapy. The mean survival of those who died was 7 months compared with 30 months for those patients still alive at follow-up. The mean age at presentation of those who died was 63 years compared with 57 years for the survivors. The gastric lymphoma patients were younger (*Table I*), there were fewer deaths among them in the observation period and they survived longer (mean 43·1 months compared with 27·6 months) than the patients with intestinal lymphoma. Life table analysis suggests a better prognosis for the gastric lymphomas and demonstrates that the majority of deaths in the whole group occurred early (*Fig.* 1).

Five of the 6 patients treated by surgery and radiotherapy at diagnosis are still alive; 9 of the 16 treated by surgery and immediate chemotherapy are alive at 12–23 months after diagnosis, 7 having died at 1–15 months; 10 of the 17 treated by surgery alone are still alive 3 years or more after diagnosis.

Discussion

This series is unique in the literature in being a study of all the gastrointestinal lymphomas diagnosed in a defined population over 6 years. The high proportion of elderly patients largely explains the high short term mortality. The disease was much more frequently localized to the gastrointestinal tract than in the large series of non-Hodgkin's lymphomas of Jones and his colleagues (1973), where only 30 per cent of gastrointestinal cases were staged as IE, IIE and IIIE, but previous smaller surgical series showed localized disease to be common (Azzopardi and Menzies, 1960; Naqvi et al., 1969). In these latter series from specialist centres a considerable element of selection was present.

The high incidence of emergency presentation of gut lymphomas, their large size and the difficulty in their radiological diagnosis have been noted previously (Dawson et al., 1961; Joseph and Lattes, 1966). These findings are explained by the lateral spread of lymphoma within the submucosal plane, sparing the muscular coat until late in the disease, in contrast to carcinoma.

Gastric lymphoma represents only 1–2 per cent of malignant gastric tumours. The tumour mimics benign or malignant ulceration. In our hands, endoscopy proved a more useful investigation than radiology. It is difficult to distinguish gastric lymphoma from carcinoma at operation. The male predominance in the gastric lymphomas has been noted by others (Loehr et al., 1969; Hertzer and Hoerr, 1976).

Prodromal symptoms are relatively uncommon in small bowel lymphoma. A small proportion may present with malabsorption (Isaacson and Wright, 1978), of whom some will have adult or lifelong coeliac disease (Harris et al., 1967; Brunt et al., 1969). In our series, only 2 were thought to have this association. A striking feature was the high incidence of perforation, as noted by others (Irvine and Johnstone, 1955). In this respect, small bowel lymphoma contrasts with Crohn's disease, with which confusion is common, and in which perforation is relatively rare. Differentiation from Crohn's disease is often difficult, especially when the lymphoma causes mesenteric thickening and node enlargement at the terminal ileum, but distinction is therapeutically very important. Further diagnostic difficulty occurs in distinguishing small bowel lymphoma from carcinoma and carcinoid, though lymphomas often involve longer segments and are frequently multiple. One technique for attempting rapid differentiation of lymphoma from carcinoma at operation is that of imprinting of the opened tumour on glass slides, stained by Romanowsky stains. We have found this reliable in the few cases studied and we hope to test this method further.

Preoperative diagnosis of gastrointestinal lymphoma, even in non-emergency cases, was rare in our experience. However, there was a suspicion of malignant disease in most patients and this meant that major elective surgery was undertaken. Complete surgical excision offers the best chance of long-term disease-free survival (Peckham and McElwain, 1977). Resection was usually feasible although it did involve considerable technical difficulties in dealing safely with thickened intestinal mesentery. When the diagnosis of lymphoma is suspected at operation, full pathological staging, including liver and node biopsy, should be carried out if at all possible. This avoids the need for a 'second look' laparotomy, which is often impossible in an elderly, debilitated patient.

The operative mortality of 9 per cent compared favourably with that in the earlier series of Navqi et al. (1969), who quoted a figure of 19 per cent: however, most of those deaths occurred before 1950. Recurrence was commoner in those with small bowel tumours and in those with tumours originally noted to be multifocal, but recurrence was not invariably fatal, as has been suggested by Bush (1974). Gastric lymphomas had a better prognosis than those in the intestine.

In a small series, with a short follow-up period, it is not possible to draw firm conclusions on the results of treatment. There is certainly a group of patients whose tumours affect all parts of the gut, who do badly irrespective of the type of treatment and who die within 18 months. Our figures show that some patients do very well with surgery alone, or with postoperative radiotherapy alone, but these are probably favourable cases from the start. In the planning of rational treatment it is vital to have adequate biopsy material. It is therefore important for the surgeon to keep the possibility of lymphoma in mind. In suspicious circumstances it is easy to obtain biopsies of liver and lymph nodes and these can be of great value in planning treatment.

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References

AZZOPARDI J. G. and MENZIES T. (1960) Primary malignant lymphoma of the alimentary tract. *Br. J. Surg.* **47**, 358–366.

BRUNT P. W., SIRCUS W. and MACLEAN N. (1969) Neoplasia and the coeliac syndrome in adults. *Lancet* **1**, 180–184.

BUSH R. S. (1974) Primary lymphoma of the gastrointestinal tract. *JAMA* **228**, 1291–1294.

BUSH R. S. and ASH C. L. (1969) Primary lymphoma of the gastrointestinal tract. *Radiology* **92**, 1349–1354.

CARBONE P. P., KAPLAN H. S., NUSSHOFF K. et al. (1971) Report of the committee on Hodgkin's disease staging classification. *Cancer Res.* **31**, 1860–1861.

DAWSON I. M., CORNES J. S. and MORSON B. C. (1961) Primary malignant lymphoid tumours of the intestinal tract. *Br. J. Surg.* **49**, 80–89.

HARRIS O. D., COOKE W. T., THOMPSON H. et al. (1967) Malignancy in adult coeliac disease and idiopathic steatorrhoea. *Am. J. Med.* **42**, 889–912.

HERTZER N. R. and HOERR S. O. (1976) An interpretive review of lymphoma of the stomach. *Surg. Gynecol. Obstet.* **143**, 113–118.

IRVINE W. T. and JOHNSTONE J. M. (1955) Lymphosarcoma of the small intestine. *Br. J. Surg.* **42**, 611–618.

ISAACSON P. and WRIGHT D. H. (1978) Intestinal lymphoma associated with malabsorption. *Lancet* **1**, 67–70.

JONES S. E., FUKS Z., BULL M. et al. (1973) Non-Hodgkin's lymphomas: clinicopathological correlation in 405 cases. *Cancer* **31**, 806–823.

JOSEPH J. I. and LATTES R. (1966) Gastric lymphosarcoma. *Am. J. Clin. Pathol.* **45**, 653–669.

LEWIN K. J., RANCHOD M. and DORFMAN R. F. (1978) Lymphomas of the gastrointestinal tract. *Cancer* **42**, 693–707.

LOEHR W. J., MUJAHED Z., ZAHN F. D. et al. (1969) Primary lymphoma of the gastrointestinal tract. *Ann. Surg.* **170**, 232–238.

NAQVI M. S., BURROWS L. and KARK A. E. (1969) Lymphoma of the gastrointestinal tract. *Ann. Surg.* **170**, 221–231.

PECKHAM M. J. and MCELWAIN T. J. (1977) The management of malignant lymphomas. *Recent Adv. Haematol.* **2**, 263–287.

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Pneumatosis coli and sigmoid volvulus: a report of 4 cases

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SUMMARY

Pneumatosis coli is an uncommon disease which is frequently misdiagnosed and inappropriately treated. The condition can usually be managed conservatively but complications requiring surgical treatment are occasionally encountered. We describe 4 patients with pneumatosis coli and associated volvulus of the sigmoid colon. Some of the factors that may have contributed to pneumocyst formation in these 4 patients are discussed with reference to recent advances in our understanding of the pathogenesis of pneumatosis coli.

PNEUMATOSIS coli is an uncommon disease of unknown aetiology in which multiple gas-filled cysts are encountered within the wall or mesentery of the large bowel. In a review of the literature, Koss (1952) found that only 47 of the 213 reported cases of pneumatosis cystoides intestinalis (PCI) had lesions in the colon, and in only 13 of these were pneumocysts restricted to the large bowel alone. More recently a change in the overall pattern of the disease appears to have occurred, with a predilection for the gas cysts to affect the left hemicolon, without small intestinal involvement (Wyatt, 1975).

Pneumatosis coli most commonly occurs as a primary idiopathic disorder, but a secondary form of the disease has been described in association with a variety of conditions including obstructing and ulcerative lesions of the colon, inflammatory bowel disease and after trauma (Wertkin et al., 1976). There are a number of reports which document the resolution of secondary pneumatosis coli with adequate treatment of the associated gastrointestinal lesion (Wyatt, 1975), and high flow oxygen therapy has provided a safe form of treatment for patients with symptomatic pneumatosis coli whether primary or secondary (Forgacs et al., 1973; Down and Castleden, 1975; Holt and Heading, 1978). Surgery is thus only indicated in the event of complications such as volvulus, intestinal obstruction or severe rectal bleeding (Broecker and Moore, 1977; Thomson et al., 1977).

We describe 4 patients in whom pneumatosis coli was associated with a twisted segment of the large bowel and discuss possible aetiological mechanisms.

Case reports

Case 1: A 38-year-old woman presented with a 10-month history of diarrhoea, lower abdominal pain, mucus discharge and slight intermittent rectal bleeding. A clinical diagnosis of ulcerative colitis was made and treatment commenced with oral sulphasalazine. Subsequent barium enema, sigmoidoscopy and biopsy demonstrated typical changes of pneumatosis coli without evidence of ulcerative colitis. The patient was referred to the gastrointestinal unit for further treatment and assessment. On admission to hospital clinical examination was normal. Colonoscopy revealed clusters of gas-filled cysts commencing 18 cm from the anus. A 5-day course of intermittent high flow oxygen therapy using a modification of the method of Down and Castleden (1975) produced a remission of symptoms. Colonoscopy demonstrated a considerable reduction in the number of gas cysts, without complete resolution.

Six months later, diarrhoea and mucus discharge recurred in association with intermittent cramp-like lower abdominal pain. A double contrast barium enema at this stage demonstrated typical changes of pneumatosis coli restricted to a redundant loop of sigmoid colon (*Fig.* 1). Repeat sigmoidoscopy and biopsy confirmed the presence of pneumatosis coli. Oral ampicillin was given (250 mg four times daily) for 2 weeks (Holt et al., 1978), but a subsequent double contrast barium enema examination showed no change.

At laparotomy a very long pelvic loop of colon was found with mesenteric striation suggesting previous torsion. There were numerous subserosal and submucosal gas cysts within the loop, which tapered to normal bowel at both ends. The diseased segment of bowel was resected (*Fig.* 2) and the patient made a good postoperative recovery. She remains well 9 months after operation.

Case 2: A 72-year-old woman was referred in November 1978 with a 7-week history of lower abdominal pain relieved by defaecation. She complained also of occasional diarrhoea, tenesmus, rectal bleeding and mucus discharge and she had noticed intermittent abdominal distension.

In 1967 a barium enema examination performed because of constipation had been found to be normal. A diagnosis of endogenous depression was made. The patient developed diarrhoea with blood and mucus in 1974 but a barium enema was negative.

On this occasion examination was normal apart from generalized gaseous distension of the abdomen. Sigmoidoscopy revealed 'polypoid structures' thought to be a probable carcinoma, but the histopathology was typical of pneumatosis coli. Barium enema demonstrated a redundant sigmoid colon in a position of potential volvulus and containing numerous gas cysts. The lower descending colon appeared normal but there was an area of pneumatosis distal to the splenic flexure.

At laparotomy a redundant sigmoid and descending colon was found containing numerous gas cysts. The mesentery was scarred, suggesting previous torsion. A left hemicolectomy was performed and the patient made an uneventful recovery.

Case 3: A 79-year-old woman was admitted to hospital with a 1-week history of abdominal distension and constipation. Two years earlier she had been admitted with similar symptoms which were related to sigmoid volvulus, confirmed by plain abdominal X-rays, and sigmoidoscopic reduction of the volvulus had been achieved. Clinical examination at the time had revealed gross gaseous abdominal distension; digital examination of the rectum had been normal.

A plain abdominal X-ray at the present admission indicated a volvulus of the sigmoid colon, which was confirmed at laparotomy. At operation a twisted and enormously dilated loop of pelvic colon was noted to be studded with numerous gas cysts typical of pneumatosis coli. The remainder of the large bowel was normal. After decompression of the pelvic colon, a Paul Mikulicz resection was performed. Pathological examination of the resected loop demonstrated typical macroscopic and microscopic features of pneumatosis coli. The patient died suddenly on the seventh postoperative day from myocardial infarction.

Case 4: An 80-year-old woman was admitted with a 3-week history of rectal bleeding and mucus discharge. Four years earlier a cerebral thrombosis had resulted in right hemiplegia.

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In the week prior to admission she had had absolute constipation with abdominal pain and intermittent vomiting. Examination revealed advanced congestive cardiac failure, abdominal distension and a large mass in the left hypochondrium. Plain abdominal X-rays showed dilated bowel in the left hypochondrium, which was considered to represent a sigmoid volvulus. The patient was unfit for operation and her condition deteriorated, culminating in her death 3 days after admission. Post-mortem examination revealed rheumatic valvular heart disease affecting the mitral and aortic valves with evidence of gross cardiac failure. The sigmoid colon was obstructed by a 20-cm length of bowel affected by pneumatosis coli. Histology of the affected segment of bowel demonstrated cystic spaces lined by flattened cuboidal cells and occasional giant cells, consistent with pneumatosis coli.

Discussion

The aetiology of pneumatosis cystoides intestinalis has been debated for many years. A number of hypotheses have been put forward to explain the pathogenesis of the condition in humans, these theories often being derived from the known association of PCI with various disease states. Koss, in his major review (1952), drew attention to the then common association with peptic ulceration and pyloric stenosis, and concluded that a mucosal breach could allow gas under pressure to be forced into the submucosal tissues, thereby creating gas cysts. The observation of an association between PCI and chronic obstructive airways disease (Doub and Shea, 1960) led to the suggestion that, following alveolar rupture, air might dissect from the thorax, travel along the adventitia of the great vessels and hence to the mesentery and wall of the bowel. This theory received some support from experimental work in dogs (Keyting et al., 1961), but both these hypotheses fail to take account of the absence of these associated conditions in a large proportion of patients, nor do they explain the primary form of the disease.

Earlier workers have favoured a bacterial causation (Naeslund, 1924; Nitch, 1924; Berglund, 1939), and Nitch described a similar condition affecting swine in epidemic form in summer. The presence in the cysts of hydrogen, an element produced in the body only by bacterial metabolism, provided further evidence that bacteria were involved. We have recently demonstrated a specific abnormality of breath hydrogen excretion in patients with PCI (Gillon et al., 1979), implying constant abnormal gas production by bacteria and providing evidence that this may be a major aetiological factor in the production and maintenance of gas cysts. The bacterial theory has also been supported recently by the experimental induction of pneumatosis in rats using various species of clostridia (Yale and Balish, 1976) and by the observation of resolution of the disease following antibiotic treatment (Wandtke et al., 1977; Holt et al., 1978). Furthermore, quantitative and qualitative bacteriological studies of the cyst walls and colonic mucosa in patients with pneumatosis coli, both before and after oxygen therapy, have revealed the presence of anaerobic organisms which may be present in the normal colonic flora (Holt and Heading, 1978).

The 4 patients described here demonstrate that volvulus of the sigmoid colon may complicate pneumatosis coli and only three separate reports of this association have been documented since the account by Koss (1952) (Frimann-Dahl, 1974; Shallal et al., 1974; Wertkin et al., 1976). The coexistence of sigmoid volvulus and pneumatosis coli is therefore rare. However, a similar situation has been observed in patients who have undergone jejunoileal bypass for morbid obesity (Martyak and Curtis, 1976;

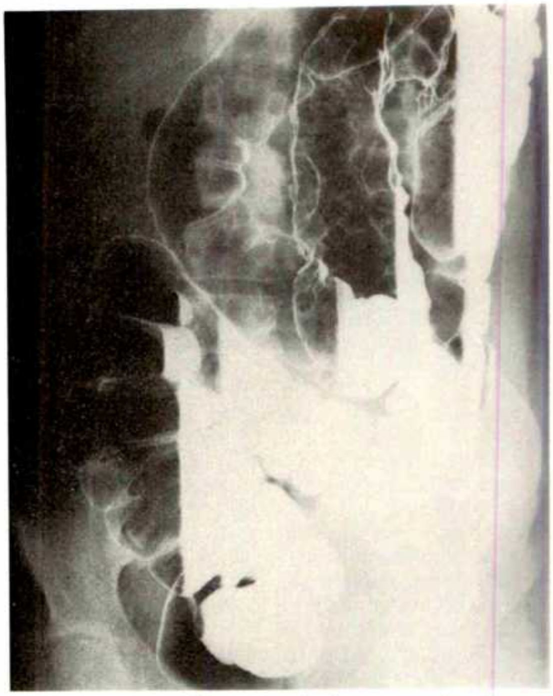

Fig. 1. *Case* 1. Double contrast barium enema showing gas cysts confined to redundant loop of sigmoid colon.

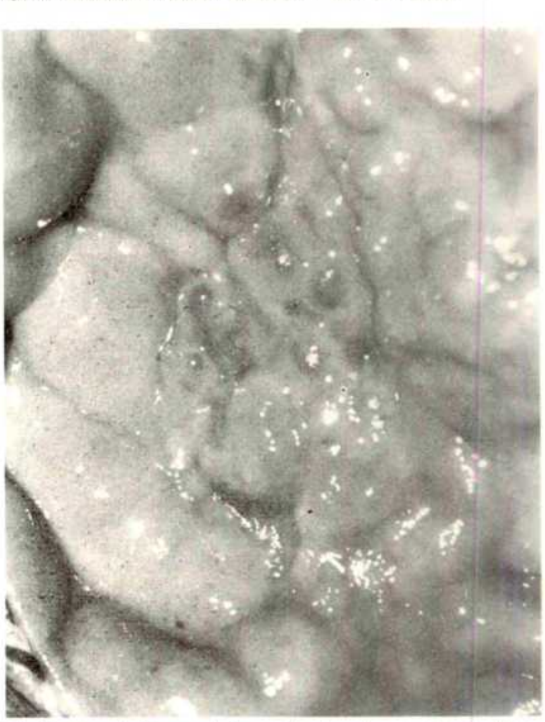

Fig. 2. *Case* 1. Resected sigmoid colon showing typical gas cysts with pneumatosis coli.

Table I: DETAILS OF 4 PATIENTS WITH SIGMOID VOLVULUS AND PNEUMATOSIS COLI

Case	Age (yr)	Sex	History of preceding pneumatosis	Diagnostic investigations	Misdiagnosis	Outcome
1	38	F	16 mth	Barium enema, colonoscopy and biopsy	Yes (ulcerative colitis)	Sigmoid resection. Full recovery
2	72	F	No	Barium enema, sigmoidoscopy and biopsy	Yes (carcinoma)	Left hemicolectomy. Full recovery
3	79	F	No	Plain film of abdomen (laparotomy)	No	Sigmoid resection. Post-operative death
4	80	F	No	Plain film of abdomen (post-mortem diagnosis of pneumatosis)	No	Died

Menguy, 1976; Passaro et al., 1976). In these patients volvulus and partial obstruction occurred at the insertion of the distal end of the bypassed small intestine into the pelvic colon and cystic pneumatosis appeared to be confined to this bypassed loop. The authors proposed that the cysts were caused by gas under pressure within the obstructed loop being forced through the mucosal breach at the anastomotic line and into the submucosa.

Passaro suggested the term 'bypass enteritis' for this condition, on the assumption that colonization of the bypassed loop by colonic bacteria was responsible for gas production, and 2 of his patients apparently responded to antibiotic therapy. Pneumatosis would therefore appear to be a secondary phenomenon in these patients. Frimann-Dahl (1974) likewise considered that his patient developed pneumatosis as a result of chronic volvulus of the sigmoid colon producing secondary mucosal ulceration and allowing gas to enter the tissue planes. A similar observation was made by Nelson (1972), who described a patient with caecal volvulus and radiologically demonstrable gas within the wall of the obstructed caecum. Histological examination showed a fulminant infection of the caecal wall with clostridial gas-forming organisms, presumably secondary to strangulation.

The diagnosis of pneumatosis coli had, however, been made some time before the development of sigmoid volvulus in the first patient described above, and in *Case* 2 the pneumocysts extended beyond the loop of sigmoid colon which had undergone volvulus. There seems little doubt that in these circumstances the volvulus was secondary to pneumatosis. In *Cases* 3 and 4 the possibility exists that volvulus was the primary event, since these patients had presented as emergencies with intestinal obstruction and no preceding history of pneumatosis coli (*Table I*).

The nature of the presenting symptoms in patients with pneumatosis coli frequently results in surgical referral. Misdiagnosis is common (Broecker and Moore, 1977), but an increasing awareness of the condition should allow surgeons to avoid inappropriate surgical intervention (Thomson et al., 1977). Conservative therapy with high flow oxygen is the preferred treatment for symptomatic patients, and surgical resection, which may be followed by recurrence of extensive disease (Thomson et al., 1977), is therefore usually unnecessary. Nevertheless, as our 4 cases show, the rare combination of pneumatosis coli and sigmoid volvulus is potentially dangerous, and we believe that surgical resection is the treatment of choice in these circumstances. •

Acknowledgement

We wish to thank Mr D. C. Thomson, Consultant Surgeon at Peel Hospital, Galashiels, for allowing us to present details of his patient (*Case* 3).

References

BERGLUND S. (1939) Roentgen diagnosis of pneumatosis cystoides intestinorum hominis. *Acta Radiol.* **20**, 401.

BROECKER B. H. and MOORE E. E. (1977) Pneumoperitoneum due to pneumatosis cystoides intestinalis in idiopathic megacolon. *JAMA* **237**, 1963.

DOUB H. P. and SHEA J. J. (1960) Pneumatosis cystoides intestinalis. *JAMA* **172**, 1238–1242.

DOWN R. H. L. and CASTLEDEN W. M. (1975) Oxygen therapy for pneumatosis coli. *Br. Med. J.* **1**, 493.

FORGACS P., WRIGHT P. H. and WYATT A. P. (1973) Treatment of intestinal gas cysts by oxygen breathing. *Lancet* **1**, 579–582.

FRIMANN-DAHL J. (1974) *Roentgen Examination in Acute Abdominal Disease*, 3rd ed. Springfield, Ill., Thomas, pp. 55–59.

GILLON J., TADESSE K., LOGAN R. F. A. et al. (1979) Breath hydrogen in pneumatosis cystoides intestinalis. *Gut.* (In the press.)

HOLT S. and HEADING R. (1978) Observations on the treatment of primary pneumatosis coli. *Proc. Br. Soc. Gastroenterol.*

HOLT S., STEWART I. C., HEADING R. C. et al. (1978) Resolution of primary pneumatosis coli. *J. R. Coll. Surg. Edinb.* **23**, 297–300.

JONES J. C. T. (1948) Gas cysts in the intestine. *Br. J. Surg.* **36**, 49–50.

KEYTING W. S., MCCARVER R. R., KOVARICK J. L. et al. (1961) Pneumatosis intestinalis: a new concept. *Radiology* **76**, 733–741.

KOSS L. G. (1952) Abdominal gas cysts (pneumatosis cystoides intestinorum hominis): an analysis with a report of a case and a critical review of the literature. *Arch. Pathol.* **53**, 523–549.

MARTYAK S. N. and CURTIS L. E. (1976) Pneumatosis intestinalis: a complication of jejunoileal bypass. *JAMA* **235**, 1036.

MENGUY R. (1976) Pneumatosis intestinalis after jejunoileal bypass. *JAMA* **236**, 1721–1723.

NAESLUND J. (1924) Zur Kenntnis der Pneumatosis Cystoides intestinorum: Pathologisch-anatomische und experimentelle Studien. Thesis (Uppsala), Stockholm.

NELSON S. W. (1972) Extra-luminal gas collections due to diseases of the gastrointestinal tract. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **115**, 225–248.

NITCH C. A. R. (1924) Cystic pneumatosis of the intestinal tract. *Br. J. Surg.* **11**, 714–735.

PASSARO E. JUN., DRENECK E. and WILSON S. E. (1976) Bypass enteritis: a new complication of jejunoileal bypass for obesity. *Am. J. Surg.* **131**, 169–174.

SHALLAL J. A. et al. (1974) Pneumatosis cystoides intestinalis. *Mayo Clin. Proc.* **49**, 180–184.

THOMSON W. O., GILLESPIE G. and BLUMGART L. D. (1977) The clinical significance of pneumatosis cystoides intestinalis: a report of 5 cases. *Br. J. Surg.* **64**, 590–592.

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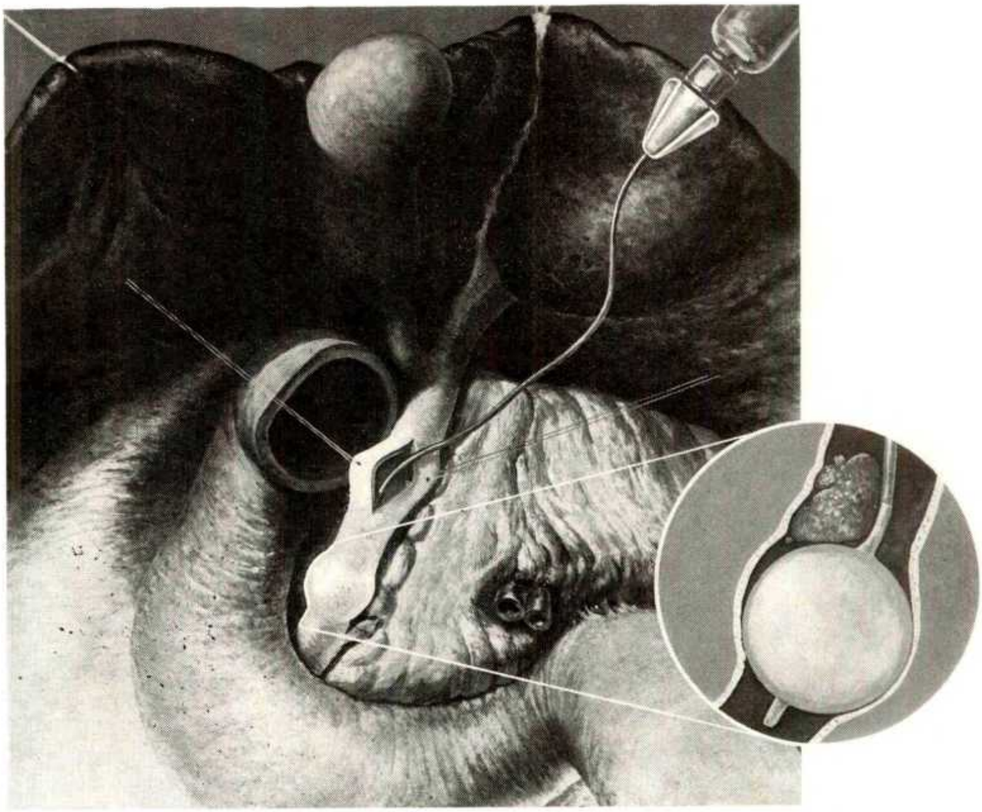

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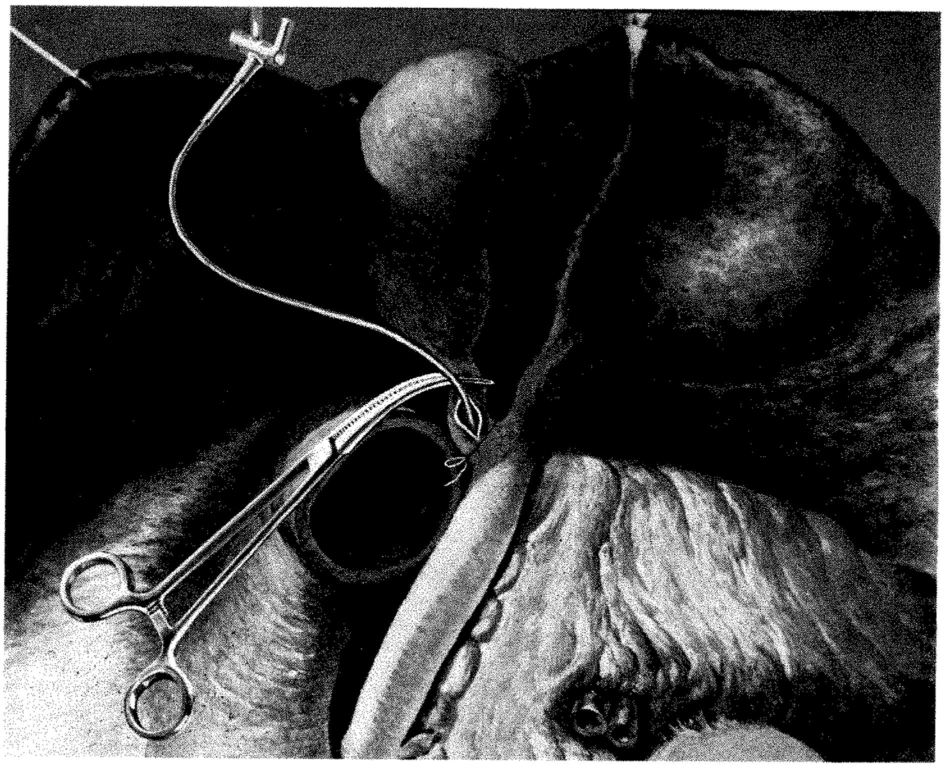

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Conclusion

The attention of surgeons performing oesophageal intubation for benign strictures is drawn to a potentially fatal complication of multiple intestinal perforation resulting from the disintegration of the Celestin oesophageal tube, which is unsuitable for long term use.

Acknowledgements

We wish to thank Professor R. Y. Calne, Mr B. B. Milstein and Mr M. Adiseshiah for permission to report these cases.

References

CELESTIN L. R. (1959) Permanent intubation in inoperable cancer of the oesophagus and cardia. *Ann. R. Coll. Surg. Engl.* **25**, 165–170.

MACKENZIE I., WHYTE A. S. and TANKEL H. I. (1976) Structural deterioration in Celestin tubes. *Br. J. Surg.* **63**, 851–852.

SIEGLE R. L., RABINOWITZ J. F. and SARASOHN C. (1976) Intestinal perforation secondary to nasojejunal feeding. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **126**, 1229–1232.

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Statistics in *The British Journal of Surgery*

It is part of the clinical scientist's stock-in-trade to use statistical methods. In many instances, and by most readers, these can be taken on trust, but in that there is a wide variety of tests and, on occasion, disagreement amongst both amateurs and professionals on the best choice, it is always wise that authors quote the method used. It is indeed journal policy to quote methods, the reason for their choice and, in the case of clinical trials, the confidence or tolerance limits of the observed results. Delay in acceptance may occur if contributors do not include these details.

Br. J. Surg. Vol. 66 (1979) 807–808

Multiple intestinal perforation due to Celestin tube

J. F. L. SHAW AND G. B. COOMBES*

SUMMARY

Two cases of multiple intestinal perforation caused by the nylon from the core of disintegrating oesophageal Celestin tubes migrating down the alimentary tract are described. It is suggested that Celestin tubes should not be used in patients likely to survive for more than a few months.

Case reports

Case 1: An 80-year-old obese man was intubated with a Celestin tube in October 1977 after regular dilatation had failed to control a 7-cm long peptic oesophageal stricture. He was able to swallow well, but in September 1978 he was readmitted with abdominal colic. At home he had passed per anum a portion of the tube attached to a nylon strand, which he had cut off at the anus. An abdominal radiograph showed evidence of small bowel obstruction, and another portion of the tube in the transverse colon. This was passed the next day, relieving his colic, and again the attached nylon strand was divided. A barium swallow showed the main portion of the Celestin tube still *in situ* in the oesophagus. Eight days later, after episodes of mild colic for one day, he developed peritonitis.

On 27 September 1978, laparotomy revealed 13 separate perforations of the small bowel, from 0·5 to 4 cm long, all on the mesenteric border at apices of loops of bowel. In the lumen was the nylon strand from the Celestin tube, which had cut through the bowel wall. The Celestin tube remnant and the nylon were removed (*Fig.* 1), and the perforations closed. Despite intensive support, the patient died of *Escherichia coli* septicaemia on the fifth postoperative day. At necropsy, linear ulcerations were seen throughout most of the small and large bowel (*Fig.* 2).

Case 2: A 72-year-old woman was treated from 1973 to 1977 with intermittent dilatation of a peptic oesophageal stricture. In August 1977 dilatation caused an oesophageal perforation, which was successfully managed conservatively, and she was subsequently intubated with a Celestin tube. She was well until August and September 1978, when she had two episodes of small bowel obstruction which were managed conservatively. Serial radiographs showed the passage of a portion of the Celestin tube along the colon, and this was subsequently passed per anum.

In October 1978 she was readmitted with peritonitis. Laparotomy disclosed six small bowel perforations along the mesenteric border, which was scarred and shortened along its whole length. A nylon strand was found along the whole length of the bowel: this was divided and removed. The perforations were closed, and she made a good recovery. Three weeks later, the proximal part of the Celestin tube was removed at oesophagoscopy. She remains well, without dysphagia.

Discussion

Celestin (1959), when describing his tube for palliating oesophageal carcinoma, emphasized that the tube was designed for the inoperable malignant stricture. The Celestin tube has, however, been used for relieving benign strictures in patients who are unsuitable for thoracotomy, and in whom self-bouginage or recurrent dilatations have failed.

The Celestin tube was developed as an improvement to the Mousseau–Barbin tube. It was originally made of polythene and had a barrel-shaped funnel. As manufactured at present, it is made of latex with a spiral nylon stiffening core. This has been found to degenerate with time, allowing the core to unravel and pass by peristalsis down the intestine (Mackenzie et al., 1976). This occurred in our cases, and resulted in multiple perforation of the small bowel as a result of a bow-string effect. A similar problem is reported in long term nasojejunal cannulation in infants (Siegle et al., 1976), where duodenal perforations may occur.

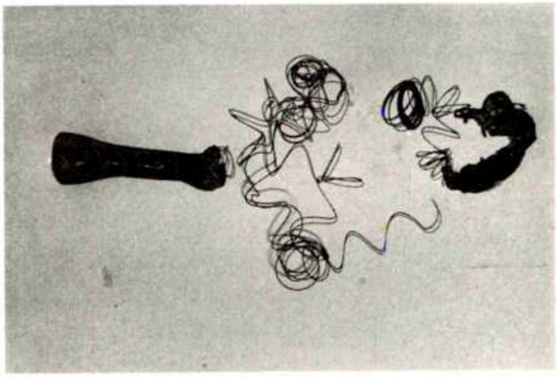

Fig. 1. The degenerate Celestin tube and nylon core after removal.

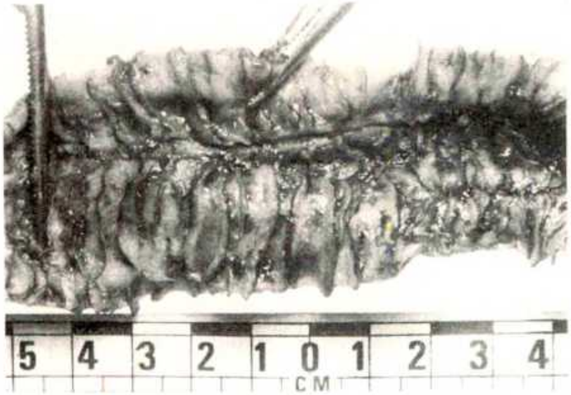

Fig. 2. Linear ulceration of the colon, resulting from the bow-string action of the nylon.

It is suggested that in patients with benign oesophageal stricture requiring intubation, the Celestin tube as at present manufactured should no longer be used. The rim of the V-shaped funnel of the Mousseau–Barbin tube may cause ulceration of the oesophageal mucosa, but the Neoplex of which it is made does not require a nylon stiffening core. Perhaps a Neoplex tube with a barrel-shaped funnel designed by Celestin would be more suitable.

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Br. J. Surg. Vol. 66 (1979) 806

Repeated haemorrhage from a terminal colostomy due to mucocutaneous varices with coexisting hepatic metastatic rectal adenocarcinoma: a case report

R. G. FINEMORE*

THE formation of varices around colostomies and ileostomies is an unusual complication of portal hypertension. In the previously reported cases cited below the cause of portal hypertension has been cirrhosis of the liver secondary to alcoholism or inflammatory bowel disease. We have found no reports describing colonic varices associated with hepatic metastatic carcinoma. The rarely reported feature of bluish skin around the stoma (Cameron and Fone, 1970) and the unreported dilated subcutaneous veins are shown in the Figure. It is well known that if hepatic replacement by neoplastic cells occurs over a long period, portal hypertension may develop with secondary development of varices. It is not known why the varices should occasionally occur in the lower rather than the upper gastrointestinal tract.

Case report

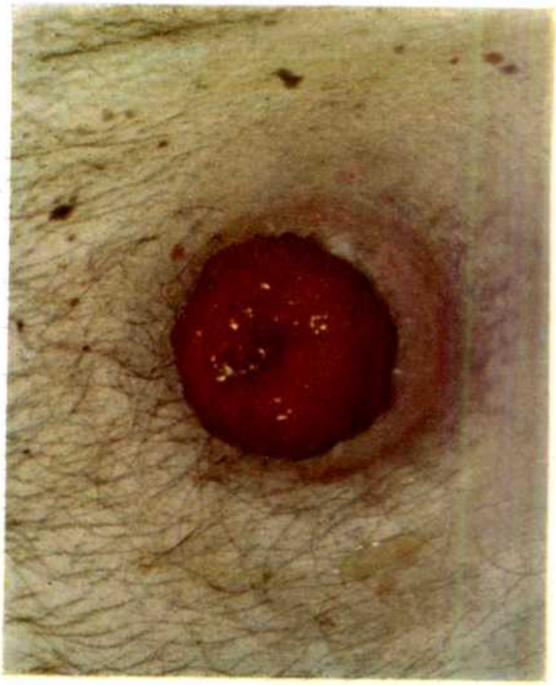
A 67-year-old man presented in April 1978 with profuse bleeding from his terminal colostomy. In February 1975 the patient had had an abdominoperineal resection and left iliac fossa terminal colostomy for a well-differentiated rectal adenocarcinoma. At operation he had had multiple metastatic deposits in the liver. There was no history of alcoholism or inflammatory bowel disease.

Two and a half years postoperatively he developed metastases in the lumbar vertebrae. These were treated with radiotherapy to the lumbar spine. He was also commenced on 5-fluorouracil and prednisone. The back pain was relieved. Three years after his abdominoperineal resection the patient presented with profuse bleeding from his colostomy. Firm pressure was applied to a pad over the colostomy and the bleeding ceased. The colostomy looked normal except for a slight swelling circumferentially around the stoma. The skin colour was normal. Digital examination of the colostomy and barium enema via the colostomy were normal. Close examination revealed the bleeding to be from the mucocutaneous junction of the stoma. Liver function tests were normal except for an elevated serum alkaline phosphatase which could have been due to the known bone metastases.

Over the next 3 months the patient had five episodes of bleeding from the colostomy, each requiring transfusion. On each occasion local pressure was applied and the bleeding ceased, except for one occasion when the bleeding point required an underrun suture at the mucocutaneous junction. Following this sodium tetradecyl sulphate solution was injected subcutaneously around the colostomy. The interval to the next episode of bleeding was prolonged—4 weeks—but when it did occur it was massive, and the patient died. Liver function tests only became deranged 6 weeks before death. During the final 2 months the swelling around the colostomy developed a bluish colour followed by the appearance of subcutaneous dilated veins.

Discussion

It would appear that the slow growth of the well-differentiated tumour in the liver was the cause of portal hypertension. However, as previous reports have suggested (Graeber et al., 1976), stomal varices occur rapidly. Bleeding from the stomal varices, when it occurs, is often massive. The management of this type of bleeding is difficult when the underlying pathological process precludes major surgery such as portasystemic venous shunt. Stomal revision has been used and reported to give adequate control of similar haemorrhages (Cameron and Fone, 1970) but we felt that this was not indicated for this patient. The varices were probably too extensive to achieve any significant lasting benefit from subcutaneous injections of sclerosing solution. We have no doubt that ligation of the bleeding point at the mucocutaneous junction controlled the bleeding when this could not be achieved by local pressure.



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References

CAMERON A. D. and FONE D. J. (1970) Portal hypertension and bleeding ileal varices after colectomy and ileostomy for chronic ulcerative colitis. *Gut* **11**, 755.

EADIE M. N., ALEXANDER-WILLIAMS J. and COOKE W. T. (1969) Bleeding from the ileostomy Caput Medusae. *Lancet* **2**, 1166.

GRAEBAR G. M., RATNER M. H. and ACKERMAN N. B. (1976) Massive haemorrhage from ileostomy and colostomy stomas due to mucocutaneous varices in patients with co-existing cirrhosis. *Surgery* **79**, 107.

HAMLYN A. N., LONZER M. R., MORRIS J. S. et al. (1974) Portal hypertension with varices in unusual sites. *Lancet* **2**, 1531.

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Correspondence to: Toowomba General Hospital, Toowomba 4350, Queensland, Australia.

WANDTKE J., SKUCAS J., SPATARO R. et al. (1977) Pneumatosis intestinalis as a complication of jejunoileal bypass. *Am. J. Radiol.* **129**, 601–604.

WERTKIN M. G., WETCHLER B. B., WAYE J. D. et al. (1976) Pneumatosis coli associated with sigmoid volvulus and colonoscopy. *Am. J. Gastroenterol.* **65**, 209–214.

WYATT A. P. (1975) Prolonged symptomatic and radiological remission of colonic gas cysts after oxygen therapy. *Br. J. Surg.* **62**, 837–839.

YALE C. E. and BALISH E. (1976) Pneumatosis cystoides intestinalis. *Dis. Colon Rectum* **19**, 107–111.

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Second Colonoscopy Congress

The Second International Congress on Colonoscopy and Diseases of the Large Bowel will be held on Thursday–Saturday, 6–8 March 1980 at the Americana Hotel, Bal Harbour, Florida. More than 60 papers, numerous panels, endoscopic movies and numerous video-taped colonoscopy and polypectomy demonstrations will be presented by a faculty of twelve speakers, headed by Drs Walter Gaisford, Hiromi Shinya, Jerome Waye and Christopher Williams.

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Br. J. Surg. Vol. 66 (1979) 809

Colonic carcinoma at the site of ureterosigmoidostomy: what is the risk?

P. M. THOMPSON, J. T. HILL AND D. A. PACKHAM*

SUMMARY

A case of colonic carcinoma arising 27 years after urinary diversion by ureterosigmoidostomy is reported. This late complication is now well recognized and increasing numbers of cases are being reported. The implications of this patient and the 31 previously reported cases are considered.

DESPITE the well-recognized complications of hyperchloraemic acidosis, chronic renal infections and urinary calculi, the ureterosigmoidostomy was for many years a popular urinary diversion and is still performed by some surgeons. With the introduction of antibiotics and improved anastomotic techniques (Woodruff et al., 1952; Leadbetter and Clarke, 1955) its popularity might have continued but for the development of the ileal conduit in the early 1950s (Bricker, 1950). Nevertheless, there are a large number of surviving patients with ureterosigmoidostomies that were performed over 25 years ago who are at risk of developing carcinoma of the colon at the site of the anastomosis.

Case report

A 30-year-old man presented with a history of vomiting and central abdominal pain for 3 days. When 3 years old he had had a total cystectomy and ureterosigmoidostomy performed for rhabdomyosarcoma of the bladder. Physical examination showed the features of a large bowel obstruction which was confirmed by plain abdominal radiographs.

An emergency laparotomy was performed which revealed an obstructing carcinoma at the ureterosigmoid junction. There were no metastases present. A transverse colostomy was performed followed 1 week later by a sigmoid colectomy and ileal conduit diversion. The colostomy was closed after 3 weeks.

Pathological examination confirmed the location of the tumour at the ureterosigmoid junction and the histology showed a mucinous adenocarcinoma including the full thickness of the muscle coat and the left ureter. The lymph nodes were not involved.

The patient was alive and well at 6-month follow-up.

Discussion

The first report of adenocarcinoma of the colon at the site of a ureterosigmoidostomy came in 1929 from Hammer. Since then there have been a further 30 cases described (Mogg, 1977; Parsons et al., 1977; Sooriyaarachichi et al., 1977).

The incidence of carcinoma after ureterosigmoidostomy is difficult to establish as the numbers are small, many patients are lost to follow-up and it is probable that some cases go unreported (Whitaker et al., 1971). However, it is clear that there is an increased risk and that the tumour occurs in a younger age group. The median age at diagnosis of colonic carcinoma after diversion is 33 years and the corresponding age in the general population is 69 (Sooriyaarachichi et al., 1977). Urdaneta and colleagues (1966) have reported 3 cases of colonic carcinoma in a series of 23 patients after 10 years and Parsons et al. (1977) had 2 cases out of 29 10-year survivors. In relating the incidence to that among the general population at the comparable age the same authors have estimated a 350- to 550-fold increase in the incidence of carcinoma in those who have undergone a ureterosigmoidostomy. From an analysis of a number of series, however, the average increased risk after 5 years has been calculated as 100 times that of the general population (Sooriyaarachichi et al., 1977).

Since the ileal loop was popularized in 1950 there has only been one recorded case of a carcinoma developing in an ileal conduit (Shousa et al., 1978). Although the same mechanism may be involved in the development of such a carcinoma in the ileum as in the colon, it would appear so far that the ileum is less susceptible.

In view of the recent cases reported we suggest that until an accurate incidence is known and the risk assessed caution should be shown in making the ureterosigmoidostomy the long term diversion of choice. In those who have had the operation performed annual sigmoidoscopy or double contrast barium enema limited to the sigmoid should be performed after 5 years.

Acknowledgements

We are grateful to Mr J. L. Dawson, under whose care the patient was admitted, for permission to report his patient.

References

BRICKER E. M. (1950) Bladder substitutions after pelvic evisceration. *Surg. Clin. North Am.* **30**, 1511–1521.

HAMMER E. (1929) Cancer du colon sigmoïde dix ans après implantation des uretères d'une vessie existrophiée. *J. Urol. Nephrol. (Paris)* **28**, 260–263.

LEADBETTER W. F. and CLARKE B. G. (1955) Five years' experience with ureteroenterostomy by the 'combined' technique. *J. Urol.* **73**, 67–83.

MOGG R. A. (1977) Neoplasms at the site of ureterocolic anastomosis. *Br. J. Surg.* **64**, 758–761.

PARSONS C. D., THOMAS M. H. and GARRETT R. A. (1977) Colonic adenocarcinoma: a delayed complication of ureterosigmoidostomy. *J. Urol.* **118**, 31–34.

SHOUSA S., SCOTT J. and POLAK J. (1978) Ileal loop carcinoma after cystoscopy for bladder exstrophy. *Br. Med. J.* **2**, 397–398.

SOORIYAARACHICHI G. S., JOHNSON R. O. and CARBONNE R. P. (1977) Neoplasms of the large bowel following ureterosigmoidostomy. *Arch. Surg.* **112**, 1174–1177.

URDANETA L. F., DUFFELL D., CREEVY C. D. et al. (1966) Late development of primary carcinoma of the colon following ureterosigmoidostomy. *Ann. Surg.* **164**, 503–513.

WHITAKER R. H., PUGH R. C. B. and DOW D. (1971) Colonic tumours following ureterosigmoidostomy. *Br. J. Urol.* **43**, 562–575.

WOODRUFF L. M., COOPER J. F. and LEADBETTER W. F. (1952) Ureteroenterostomy. Experimental studies. *J. Urol.* **67**, 873–879.

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Br. J. Surg. Vol. 66 (1979) 810–812

Postoperative hypoxaemia: oesophagectomy with gastric replacement

D. G. M. BISHOP AND K. C. McKEOWN*

SUMMARY

Pre- and postoperative arterial blood samples were analysed for oxygen partial pressure ($Pa\mathrm{o}_2$) and carbon dioxide partial pressure ($Pa\mathrm{co}_2$) in a consecutive series of 21 patients subjected to two- or three-stage oesophagectomy for carcinoma of the oesophagus. The forced vital capacity (FVC) was measured at the same time.

On the second postoperative day the $Pa\mathrm{o}_2$ showed a fall to 65 per cent of the preoperative value followed by a gradual recovery to 78 per cent on the tenth postoperative day. After 13 weeks the $Pa\mathrm{o}_2$ had recovered to 95 per cent of the preoperative value.

The $Pa\mathrm{co}_2$ decreased in the early postoperative period but had returned to the preoperative level by the tenth day. The FVC showed a trend similar to the $Pa\mathrm{o}_2$ with a reduction to 33 per cent of the preoperative value on the second postoperative day, 52 per cent on the tenth day and 85 per cent after 13 weeks.

ARTERIAL hypoxaemia after operation is usual and follows even trivial procedures. Nunn and Payne (1962) found that after minor procedures under general anaesthesia, hypoxaemia was present for several hours though the $Pa\mathrm{co}_2$ was normal, and thus they and others (Palmer and Gardiner, 1964; Palmer et al., 1965) postulated that the hypoxaemia was due not to simple hypoventilation but to a disturbance in the ventilation–perfusion relationship in the lungs.

Arterial hypoxaemia and mechanical impairment of respiratory function are greatest for upper abdominal surgery, less for lower abdominal surgery and least for non-abdominal surgery (Diament and Palmer, 1966). After upper abdominal surgery, on the first postoperative day $Pa\mathrm{o}_2$ is reduced to 80 per cent of preoperative value, after lower abdominal surgery to 90 per cent and after non-abdominal surgery to 94 per cent. Reduction in forced vital capacity (FVC) is also found but previous workers have not demonstrated a clear correlation between this and $Pa\mathrm{o}_2$.

A comparison of the effect of upper abdominal surgery and thoracoabdominal surgery of the gastrointestinal tract on $Pa\mathrm{o}_2$ (Knudsen, 1970) showed that after upper abdominal surgery the lowest value of $Pa\mathrm{o}_2$ occurred on the third day. The reductions were between 77 and 94 per cent of the preoperative value, with a mean reduction of 84 per cent. Values had returned to normal by the fourteenth day. After thoracoabdominal procedures the lowest values (66–91 per cent, mean 80 per cent) occurred between the fifth and seventh days. Preoperative levels had not been regained at 14 days when the patients were discharged.

In two-stage oesophagectomy patients are subjected to an upper abdominal incision and a right thoracic incision, and in the case of the three-stage operation, a right cervical incision also (McKeown, 1976). On the basis of previous investigations this would be expected to have a marked effect on the respiratory system. This investigation was carried out to determine the duration and severity of arterial hypoxaemia and reduction in FVC following these procedures.

Patients and methods

A consecutive series of 21 patients was investigated after two and three-stage oesophagectomy (*Table I*). Preoperatively the patients received physiotherapy and were instructed in the use of Woolf's bottles which they used pre- and postoperatively. They were also instructed in the technique of postural drainage to assist their cooperation with the physiotherapists in the postoperative period.

Patients were premedicated with Cyclimorph 0·2 mg/kg and atropine 0·4 mg/kg by intramuscular injection 1 h before operation. Anaesthesia was induced with thiopentone up to 4 mg/kg and maintained with nitrous oxide and oxygen supplemented with halothane as required. Muscular relaxation was obtained using tubocurarine. All the operations and anaesthetics were carried out by the authors.

After operation analgesia was achieved by 2-hourly intramuscular injections of 25 mg pethidine until the patient settled. All patients were given oxygen by Ventimask—28 per cent if under 60 years of age and 35 per cent if over 60 years of age. This was continued until the patient could maintain a $Pa\mathrm{o}_2$ of 6·7 kPa while breathing air.

Arterial sampling and subsequent FVC measurements were made with the patients positioned so that the chest was 45° to the horizontal. Before sampling the patients breathed room air for 90 min and no analgesic drugs were administered in the 6-hour period prior to measurement. Arterial samples were obtained from the radial artery using a Macbick arterial blood sampling kit. The analysis of the arterial blood was carried out immediately. FVC was measured immediately after the arterial sampling. Both procedures were carried out on the day before operation and on postoperative days 2, 4, 6, 10, 14, 21 and 91.

For blood gas analysis an IL 213 analyser was used and was maintained solely for this investigation. The analyser was calibrated according to the maker's instructions using standard gas mixtures. The FVC measurements were obtained with a standard Vitalograph, the best of three attempts being the value taken. The samples and measurements were all taken by one person (D. G. M. B.). Statistical analysis was by paired *t* tests.

Table I: DETAILS OF THE CASE SERIES

	Age (yr) (±s.d.)	Two-stage operation	Three-stage operation
Males	61·7±13·8	4	6
Females	67±7·5	5	6

Results

The $Pa\mathrm{o}_2$ fell sharply after operation and then gradually increased (*Fig.* 1). The value of $Pa\mathrm{o}_2$ fell significantly after operation ($P<0{\cdot}0001$) in all cases and then increased significantly after each time interval. At the end of 91 days the $Pa\mathrm{o}_2$ values were significantly below their preoperative value ($P<0{\cdot}0001$) for the female patients, but were not significantly reduced in the case of the male patients.

The value of $Pa\mathrm{co}_2$ fell after operation, but by the tenth postoperative day the values obtained were not significantly different from the preoperative value (*Fig.* 2).

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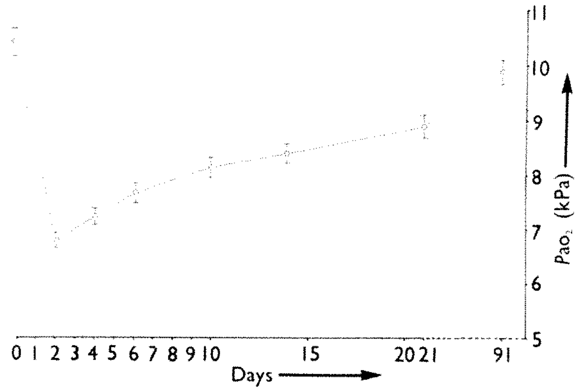

Fig. 1. Course of mean ± s.e. mean of $Pa\text{O}_2$ over time.

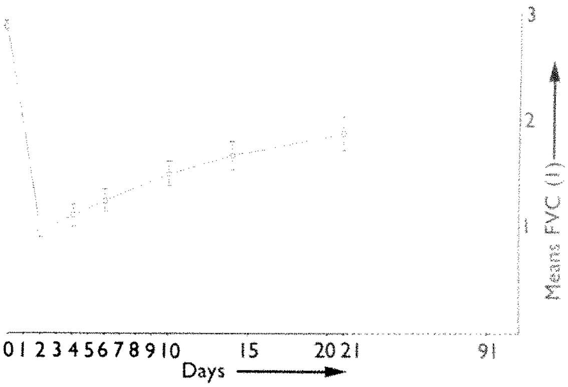

Fig. 3. Course of mean ± s.e. mean of FVC over time.

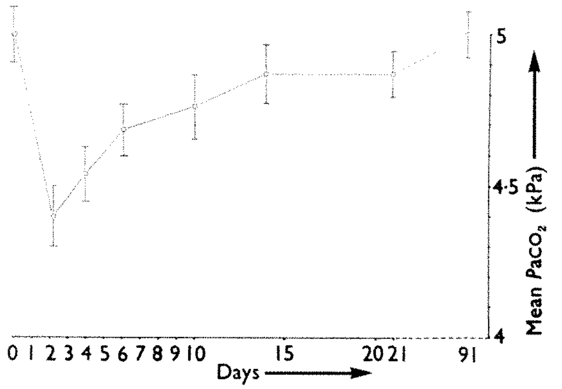

Fig. 2. Course of mean ± s.e. mean of $Pa\text{CO}_2$ over time.

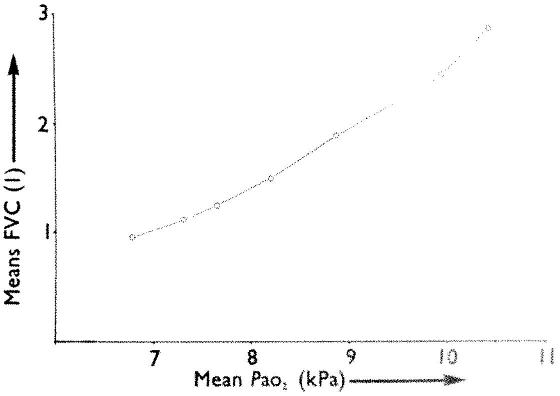

Fig. 4. Relationship between mean FVC and mean $Pa\text{O}_2$ between 1 and 91 days.

The FVC fell sharply after operation and then gradually increased (*Fig.* 3). The significance of the fall on the second postoperative day was $P < 0{\cdot}0001$ in all cases. At 91 days the value was still significantly below the preoperative value ($P < 0{\cdot}0001$).

The mean value of FVC was plotted against the mean value of $Pa\text{O}_2$ for each postoperative day (*Fig.* 4). Both values were seen to increase in a similar manner with the passage of time.

Discussion

Hypoxaemia extending beyond the immediate postoperative period has been attributed to a variety of factors.

After partial gastrectomy in patients with normal respiratory function preoperatively there is a reduction in vital capacity to 45 per cent of its preoperative value with a gradual increase to 76 per cent by the fifth postoperative day (Palmer et al., 1965). Movements of the thorax, abdomen and diaphragm can be restricted by the mechanical inefficiency caused by incision of muscles and by the restrictive effects of bandages, gut distension and pneumoperitoneum (Anscombe, 1957).

Pain from the surgical incision is associated with a decrease in vital capacity and reduction in the efficiency of coughing and the ability to make maximal inspiratory efforts. Effective pain relief would be expected to ameliorate these effects. Spence and Smith (1971) showed that segmental thoracic epidural analgesia after upper abdominal surgery reduced hypoxaemia and the alveolar–arterial oxygen difference ($D(\text{A–a})P\text{O}_2$) when compared with the use of morphine (10 mg intramuscular injection) given on patient demand. By the fifth postoperative day patients in the epidural group had achieved their preoperative $Pa\text{O}_2$ levels whereas the morphine group had not. Bromage (1967) reported that segmental thoracic epidural analgesia after upper abdominal surgery restored the vital capacity to a level between 70–100 per cent of its preoperative value and restored the functional residual capacity (FRC) to normal.

The pulmonary mechanism by which hypoxaemia is produced after operation is thought to be due to a combination of ventilation–perfusion mismatch and shunt. These in turn are secondary to changes in FRC and the closing volume (CV) (Milic-Emili et al., 1966; Spence and Alexander, 1972).

Expiration from total lung capacity to residual volume (RV) is normally accompanied by small airway closure in the dependent parts of the lung where transpulmonary pressure (TPP) is highest. The lung volume at which this occurs is the CV, which in young people normally lies close to the RV. Pain, with its attendant muscle spasm, causes an increase in TPP which results in a decrease in FRC and an increase in CV. This effect is enhanced by obesity, age and mechanical pressures due to bandages, gut distension and pneumoperitoneum. In young people small airway closure does not occur during normal tidal breathing, but in the circumstances mentioned above, or in the presence of lung disease, the CV can lie within the range of normal tidal breathing. Intermittent airway closure during tidal breathing leads to ventilation–perfusion mismatch and if TPP is high enough some small airways may remain closed throughout the respiratory cycle, resulting in shunt (Leblanc et al., 1970). It has been shown that $D(\text{A–a})Po_2$ increases as the difference between CV and FRC decreases. The $D(\text{A}-\text{a})Po_2$ also increases as the FRC decreases, and since the FRC alters more after operation than the CV, it is the more important factor of the two (Alexander et al., 1973).

The present study shows that the combination of an upper abdominal incision and right thoracic incision produces a disturbance in respiratory function that is greater in duration and extent than that produced by either of these incisions on their own. In addition to the causative factors already mentioned, there is another, unique factor present in this series, i.e. the transposed stomach, an elastic bag of variable size which is open to the atmosphere. The presence of this 'hydropneumothorax' could account for the observed reduction in the FVC below the preoperative level at 13 weeks after operation and also for the reduction in the Pao_2 of the female patients at 13 weeks. The Pao_2 of the male patients at 13 weeks had returned to preoperative values but the FVC of the male is, of course, larger to start with than that of the female.

The close association in time of changes in Pao_2 and FVC is surprising as previous investigators have not shown any simple relationships between postoperative hypoxaemia and restrictive impairment of respiratory function as shown by FVC, although the association with FRC is well known.

Acknowledgements

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References

ALEXANDER J. L., SPENCE A. A., PARIKH R. K. et al. (1973) The role of airway closure in postoperative hypoxaemia. *Br. J. Anaesth.* **45**, 34–40.

ANSCOMBE A. R. (1957) *Pulmonary Complications of Abdominal Surgery.* Chicago, Year Book.

BROMAGE P. R. (1967) Extradural analgesia for pain relief. *Br. J. Anaesth.* **39**, 721–729.

DIAMENT M. L. and PALMER K. N. V. (1966) Postoperative changes in gas tensions of arterial blood and in ventilatory function. *Lancet* **2**, 180–182.

KNUDSEN J. (1970) Duration of hypoxaemia after uncomplicated upper abdominal and thoracoabdominal operations. *Anaesthesia* **25**, 372–377.

LEBLANC P., RUFF F. and MILIC-EMILI J. (1970) Effects of age and body position on 'airway closure' in man. *J. Appl. Physiol.* **28**, 448–451.

MCKEOWN K. C. (1976) Total three-stage oesophagectomy for carcinoma of the oesophagus. *Br. J. Surg.* **63**, 259–262.

MILIC-EMILI J., HENDERSON J. A. M., DOLOVICH M. B. et al. (1966) Regional distribution of inspired gas in the lung. *J. Appl. Physiol.* **21**, 749–759.

NUNN J. F. and PAYNE J. P. (1962) Hypoxaemia after general anaesthesia *Lancet* **2**, 631–632.

PALMER K. N. V. and GARDINER A. J. S. (1964) Effect of partial gastrectomy on pulmonary physiology. *Br. Med. J.* **1**, 347–349.

PALMER K. N. V., GARDINER A. J. S. and MCGREGOR M. H. (1965) Hypoxaemia after partial gastrectomy. *Thorax* **2[illegible]**, 73–75.

SPENCE A. A. and ALEXANDER J. L. (1972) Pulmonary consequences of abdominal and thoracic surgery. *Int. Anaesthesiol. Clin.* **10**, 41–59.

SPENCE A. A. and SMITH G. (1971) Postoperative analgesia and lung function: a comparison of morphine with extradural block. *Br. J. Anaesth.* **43**, 144–148.

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Br. J. Surg. Vol. 66 (1979) 813–818

The preoperative detection of internal mammary lymph node metastases in breast cancer*

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SUMMARY

The internal mammary lymph node chain has been studied in patients with breast cancer by radioisotope imaging. The technique enabled the study of lymph node function in an area inaccessible to clinical examination or lymphography.

Thirty-four patients with breast cancer have been studied by injecting the posterior sheath of the rectus abdominis muscle, in the subcostal region, with technetium-99^{m}*-labelled stannous phytate and subsequently imaging the anterior thorax. Lymph node metastases were diagnosed in 13 patients (38 per cent) in whom a suppressed uptake of the isotope by the internal mammary lymph nodes was observed. Eighteen patients (53 per cent) had normal scans and in 3 patients (9 per cent) the examination was technically unsatisfactory. Histopathological correlation of internal mammary node biopsy with the preoperative scan confirmed the scan findings in all but one case in which this was carried out. Radioassay of internal mammary lymph nodes confirmed that the agent was localized in them and that uptake was suppressed in the presence of metastases.*

Twenty-three patients in this study underwent sequential scanning using first ^{99}*Tc*^{m}*-labelled stannous phytate and subsequently* ^{99}*Tc*^{m}*-labelled antimony sulphide colloid. The latter agent was able to demonstrate the anatomical presence of nodes when a suppressed uptake had initially been observed using* ^{99}*Tc*^{m}*-labelled stannous phytate.*

Internal mammary lymphoscintigraphy may be of value in the preoperative staging of breast cancer.

THE spread of breast cancer to the regional lymph nodes is of importance in determining the treatment of local disease by surgery and radiotherapy as well as being the most accurate prognostic indicator (Fisher et al., 1969).

The internal mammary lymph nodes (IMN) are an important site of regional lymph node spread (Handley and Thackray, 1954). One-quarter of all patients with operable breast cancer have IMN metastases. A small proportion of patients have this as the sole site of nodal metastatic disease; if this site is not taken into account, errors in staging will occur.

The IMN are not accessible to clinical examination or lymphography and so are not taken into account in preoperative staging. In order to improve this aspect of staging, IMN isotope imaging has been studied in patients with breast cancer.

Patients and methods

Thirty-four patients with breast cancer were studied; the tumours were predominantly located centrally or in the inner quadrants. Full TNM clinical staging with blood count, liver function tests, chest radiography, skeletal scintigraphy and urinary hydroxyproline estimation was carried out before treatment. IMN scanning was carried out on admission.

Technique of internal mammary lymphoscintigraphy

Single agent scan: A preparation of ^{99}Tc^{m}-labelled stannous phytate (^{99}Tc^{m} SnP) was injected into the posterior sheath of the rectus abdominis muscle in the subcostal region on the same side as the tumour (Osborne, Jewkes et al., 1978). This site of injection allows radioisotopic imaging of the IMN chain on the same side as the injection (Rossi and Ferri, 1966; Schenck, 1966). The agent was prepared from a kit (Diagnostic Isotopes Inc.) by adding 2–4 ml of sterile, pyrogen-free, sodium pertechnetate to a vial containing 10 mg of sodium phytate and 1·0 mg of stannous chloride. Three hundred microCuries of ^{99}Tc^{m} SnP in 0·2 ml were injected.

Some patients also received an injection of ^{99}Tc^{m} SnP into the contralateral posterior rectus sheath in order to image the contralateral IMN chain on the 'normal' side.

Imaging was carried out 2 h after injection.

Dual agent 'sequential' scans: Following an injection of ^{99}Tc^{m} SnP and subsequent IMN imaging 2 h later, a preparation of ^{99}Tc^{m}-labelled antimony sulphide colloid (^{99}Tc^{m} SbSC) was injected into the posterior sheath of the rectus abdominis muscle on the same side as the tumour near the site of the previous injection. A further image was obtained 2 h after this injection, the entire procedure being carried out in a 4-h period. ^{99}Tc^{m} SbSC was prepared from a kit (Philips–Duphar BV) by adding 2–4 ml of sterile, pyrogen-free sodium pertechnetate solution to a vial containing antimony trisulphate. The vial was heated in a water bath for 15 min, cooled and citrate buffer (pH 12·8) added. Three hundred microCuries of ^{99}Tc^{m} SbSC in 0·2 ml were injected.

Dual agent lymphoscintigraphy was carried out as the diagnosis of IMN metastases depends on observing a suppression of uptake of ^{99}Tc^{m} SnP and there might be doubt as to the anatomical presence of these nodes. Previous laboratory studies of experimental models (Osborne, Jeyasingh et al., 1978) have shown that lymph nodes *partially* replaced by metastatic tumour will take up ^{99}Tc^{m} SbSC and may be imaged.

Gamma camera imaging: Images of the anterior thorax and upper abdomen were obtained using a wide-field, high resolution gamma camera (NE 8960) with online computerized data processing facilities (Varian Data Analyser). Patients were imaged for 3 min using a parallel-hole collimator with a pulse height analyser setting of 140 KeV. Anatomical landmarks were shown using an americium-241 10 mCi marker to identify exactly the site of internal mammary lymph nodes. The scans were presented as a computer output image using an electrostatic plotter after suitable background subtraction.

Interpretation of lymphoscintiscans

Single agent scan: A lymphoscintiscan was interpreted as normal when localization of ^{99}Tc^{m} SnP was observed in the upper intercostal spaces in the parasternal region on the same side as the tumour (*Fig.* 1*a*). An abnormal scan, indicating the presence of lymph node metastases, was interpreted as such when a suppressed localization of the radioisotope was observed in the upper intercostal spaces in the parasternal region on the same side as the tumour (*Fig.* 2*a*). The correct placement of the injection was confirmed by visualization of the xiphoid or lower internal mammary nodes. Incorrect siting of the injection resulted in localization of the isotope in axillary or inguinal regional nodes if too superficial, or an image of the peritoneal cavity if too deep.

Dual agent 'sequential' scans: Sequential scans, imaging first after injecting ^{99}Tc^{m} SnP and subsequently after ^{99}Tc^{m} SbSC,

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* Based on a short paper presented at the Annual Meeting of the Association of Surgeons at Norwich, April 1979.

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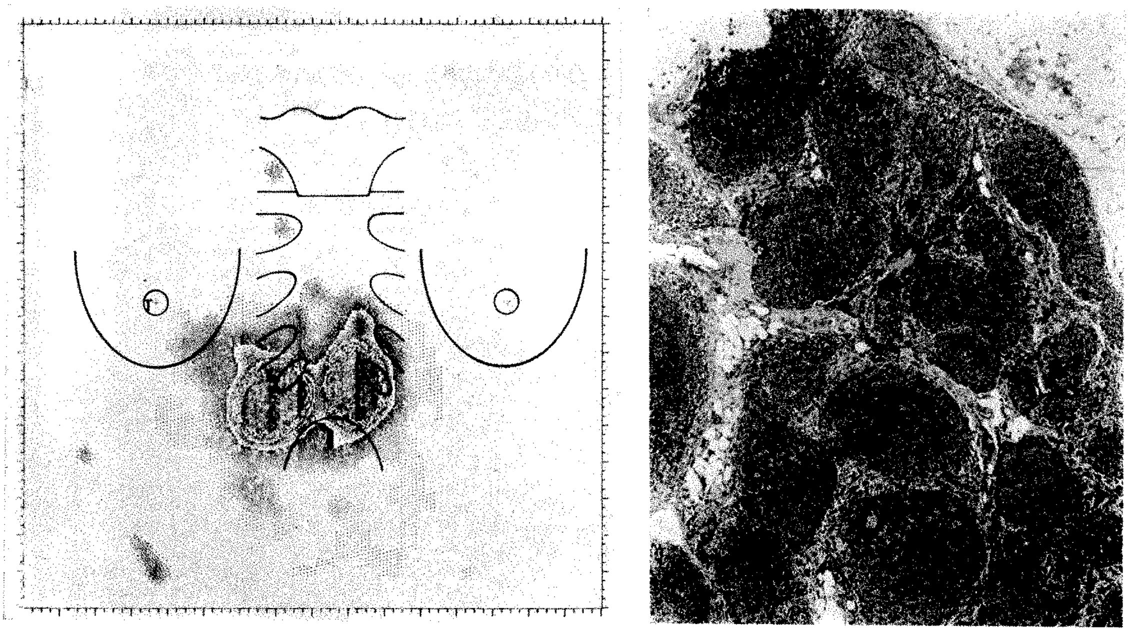

a *b*

Fig. 1. Forty-nine-year-old patient with a T2a NIb M0 carcinoma (T) in the central region of the right breast. *a*, Normal internal mammary lymphoscintiscan using ^{99}Tc^{m} SnP showing the subcostal injection site and localization of the isotope in the IMN in the upper intercostal spaces on the same side as the tumour. *b*, Low power (×33) photomicrograph of a representative serial section from the right second intercostal space internal mammary node showing normal lymph node architecture. The first intercostal space node was also normal.

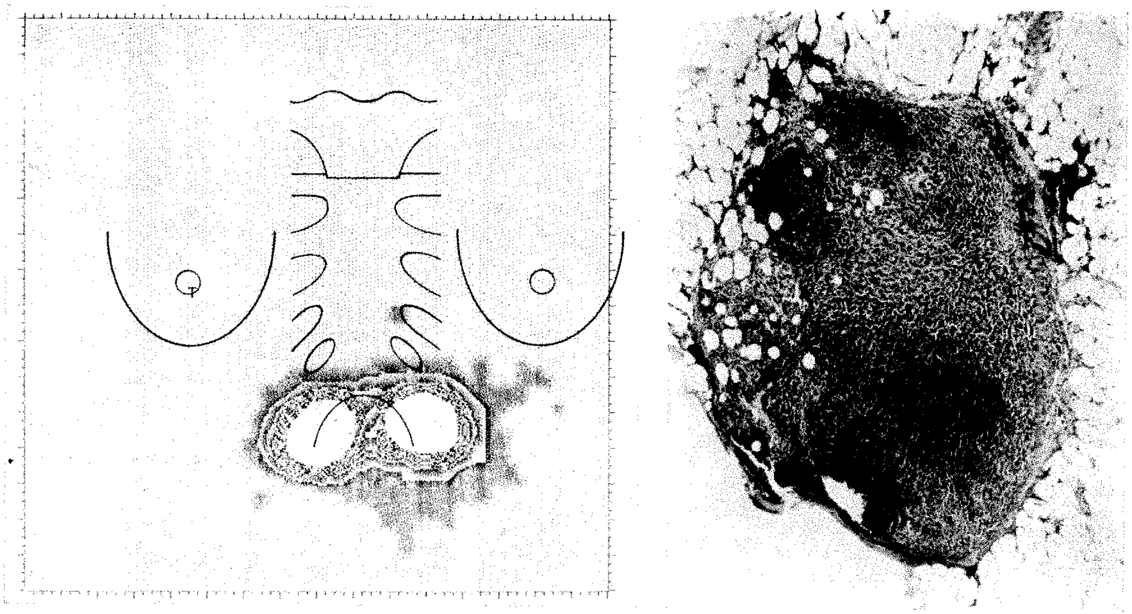

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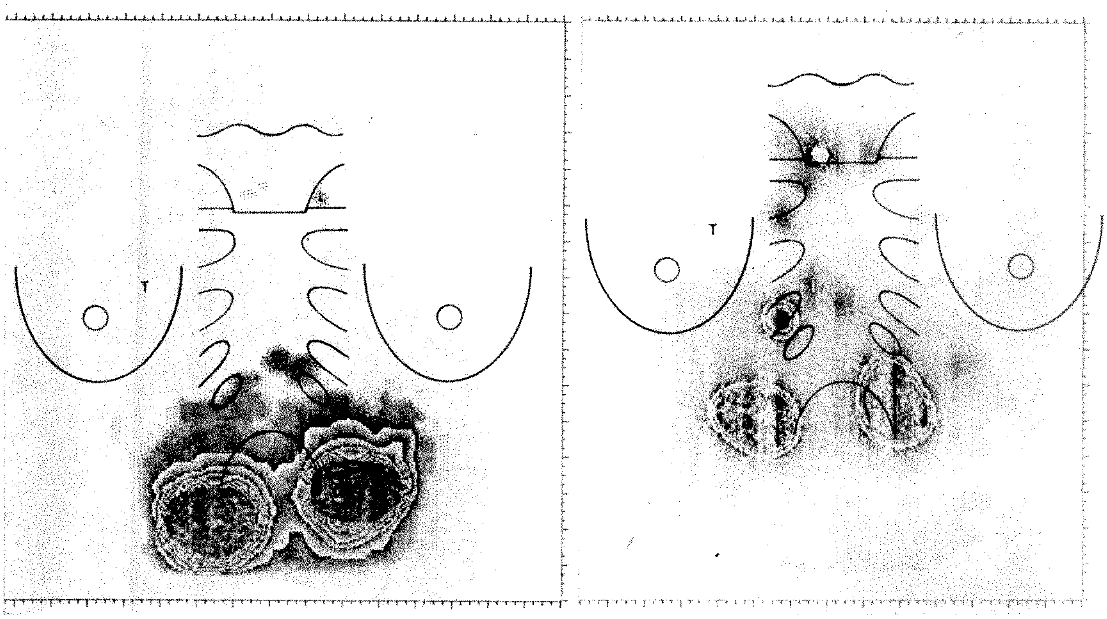
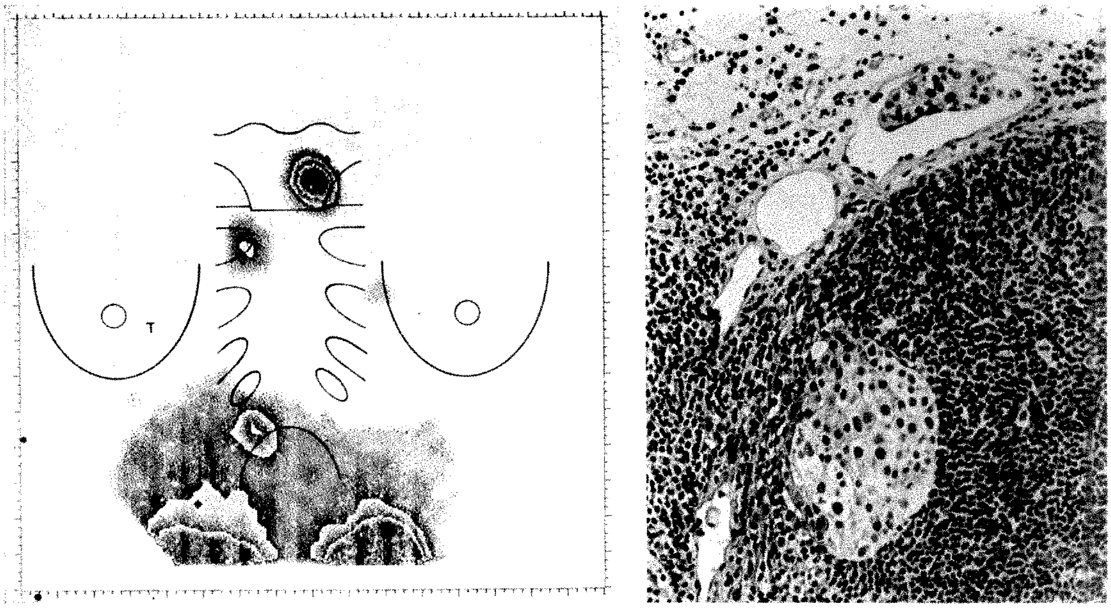
Fig. 2. Forty-seven-year-old patient with a T0 N0 M0 carcinoma (T) (mammographic abnormality) in the central region of the right breast. *a*, Abnormal internal mammary lymphoscintiscan using ^{99}Tc^{m} SnP showing absent uptake of the isotope by the IMN on the ipsilateral and contralateral sides. A lower IMN on the left is seen. *b*, Low power (×42) photomicrograph showing extensive metastatic tumour infiltration in the right second intercostal space internal mammary node. Secondary deposits were also seen in nodes from the right first and third intercostal spaces.



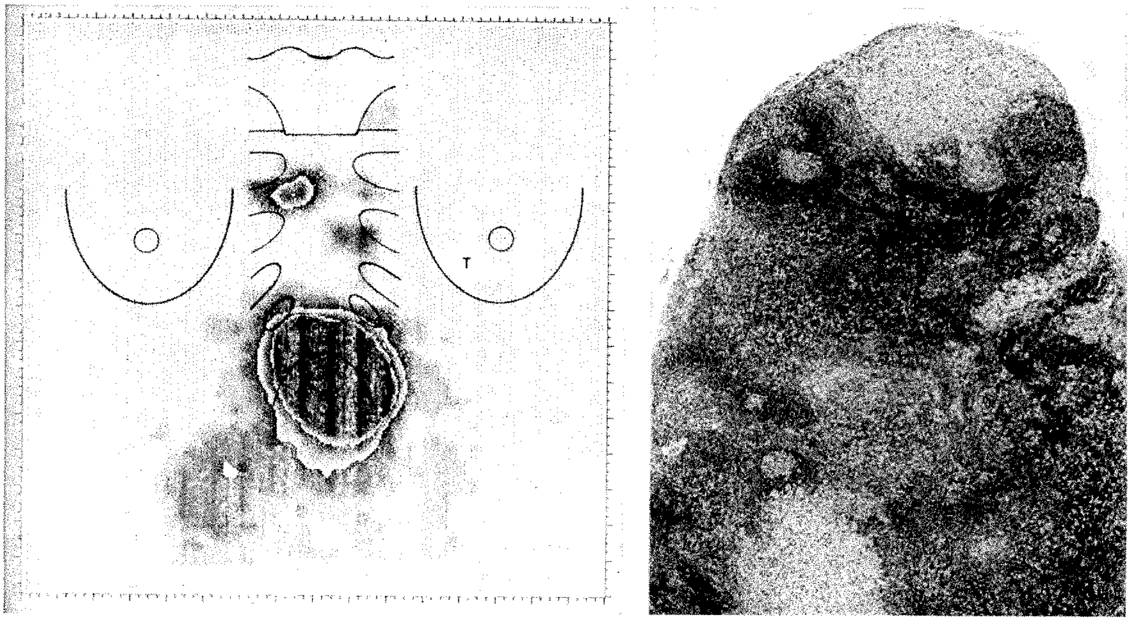
a *b*

Fig. 3. Sequential internal mammary node scan in a 46-year-old patient with T2a N0 M0 carcinoma (T) in the right upper inner quadrant. *a*, Abnormal internal mammary lymphoscintiscan using ^{99}Tc^{m} SnP showing absent uptake of the isotope by the IMN on the side of the tumour, uptake is seen on the contralateral side. *b*, Internal mammary lymphoscintiscan using ^{99}Tc^{m} SbSC now showing uptake of the isotope by the IMN on the side of tumour and a similar pattern on the contralateral side.



a *b*

Fig. 4. Forty-one-year-old patient with a T2a N0 M0 carcinoma (T) in the right lower inner quadrant. *a*, Normal internal mammary lymphoscintiscan using ^{99}Tc^{m} SnP showing a 'hot' node in the right second intercostal space. *b*, High power (×156) photomicrograph showing a subcapsular sinus micrometastasis in the right second intercostal space internal mammary node. A tumour embolus in an afferent lymphatic is also seen.



a *b*

Fig. 5. Fifty-one-year-old patient with T2a N0 M0 carcinoma (T) in the left lower inner quadrant. *a*, Normal internal mammary lymphoscintiscan using $^{99}\mathrm{Tc}^{m}$ SbSC. Uptake of the isotope is seen in the internal mammary nodes on the same side as the tumour and on the contralateral side. *b*, Low power (×22·5) photomicrograph showing two tumour metastases in the left second intercostal space internal mammary node.

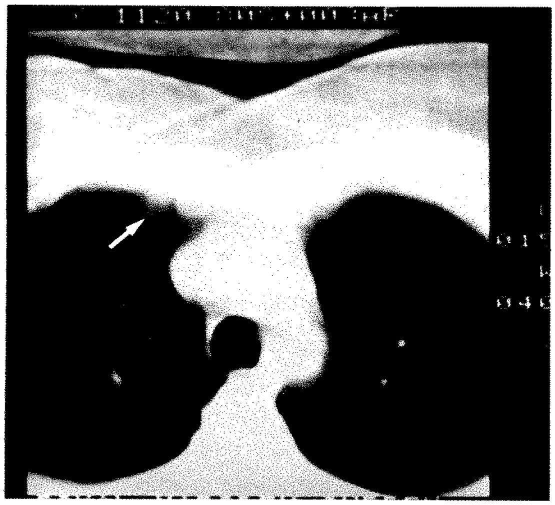


Fig. 6. Computer-assisted tomogram of the thorax of a 28-year-old patient who presented with a right axillary node mass. Sequential scanning suggested IMN metastases. The arrow points to a mass projecting into the anteromedial part of the right hemithorax at the level of the second intercostal space, suggesting enlargement of an internal mammary node.

Table I: INTERNAL MAMMARY LYMPH NODE RADIOASSAY FOLLOWING $^{99}\mathrm{Tc}^{m}$ SnP SCANNING EXPRESSED AS SPECIFIC ACTIVITIES (c min^{-1} g^{-1})

Target (IMN) (c min^{-1} g^{-1})	Non-target (pectoral muscle) (c min^{-1} g^{-1})	Target: non-target ratio	IMN histology
167 930	194	866 : 1	Normal
341	383	0·89 : 1	Metastasis
392	383	1·02 : 1	Metastasis

were interpreted on the basis of the previous laboratory studies. A sequential scan was interpreted as being normal if there was localization of both agents in a similar pattern in the upper intercostal spaces in the parasternal region on the same side as the tumour. An abnormal scan, indicating the presence of IMN metastases, was interpreted as such if a suppressed uptake of $^{99}\mathrm{Tc}^{m}$ SnP was observed on the first scan, the subsequent $^{99}\mathrm{Tc}^{m}$ SbSC scan showing uptake by the upper IMN on the same side as the tumour (*Fig.* 3), thereby confirming the anatomical presence of nodes.

Lymph node radioassay

In a small number of cases where single agent IMN scanning using $^{99}\mathrm{Tc}^{m}$ SnP was carried out within 24 h of operation, lymph nodes were radioassayed in a well scintillation counter with control tissue of pectoral muscle (*Table I*). The background was subtracted and the results expressed as the specific activity —radioactive counts per unit time per unit wet weight of tissue (counts per minute per gramme—c min^{-1} g^{-1}).

Histopathological correlation

Internal mammary lymph nodes on the same side as the tumour were biopsied at the time of mastectomy in suitable operable patients. The nodes were fixed in formol saline, step-cut (20 μm) serially sectioned and stained with haematoxylin and eosin. Sections were examined for metastases.

Results

Single agent scans

Thirty-four patients with breast cancer were studied using $^{99}\mathrm{Tc}^{m}$ SnP. Eighteen patients (53 per cent) had normal scans and 13 patients (38 per cent) had abnormal scans, suggesting the presence of IMN metastases. Three patients (9 per cent) had a technically unsuccessful scan due to misplacement of the injection. No complications were observed in this study.

Fifteen patients (50 per cent) with technically satisfactory scans (11 normal and 4 abnormal) had histopathological correlation between the internal mammary nodes biopsied at operation and the preoperative scan. Ten out of 11 *normal* scans were confirmed to be correct (e.g. *Fig.* 1), one was incorrect and found to have a subcapsular sinus micrometastasis on serial section (*Fig.* 4). Four patients with *abnormal* scans all were confirmed histologically to have internal mammary node metastases (e.g. *Fig.* 2). The patient illustrated in *Fig.* 2 had a T0 N0 M0 centrally positioned infiltrating carcinoma in the right breast which was impalpable and was detected in a screening programme by mammography. Biopsy of the IMN from the right second and third intercostal spaces confirmed the presence of metastases, the axillary lymph nodes were not involved.

In those patients in whom the contralateral IMN were scanned (e.g. *Fig.* 2) suppressed uptake was observed, but biopsy of these nodes to confirm the presence of contralateral IMN spread of tumour was not possible as these nodes are not accessible during mastectomy.

Dual agent 'sequential' scans

Twenty-three patients underwent sequential scanning using ^{99}Tc^{m} SnP and ^{99}Tc^{m} SbSC. Eleven patients (46 per cent) had normal scans where both agents showed a similar localization of the isotope in the upper intercostal spaces on the same side as the tumour, 8 patients (33 per cent) had an abnormal scan where a different pattern of uptake was observed between the two agents (*Fig.* 3). Five patients (21 per cent) had uninterpretable scans due to misplacement of one of the injections. In this series 8 patients with technically satisfactory scans (6 normal and 2 abnormal) had histopathological correlation of the internal mammary nodes biopsied at operation with the preoperative scan. The presence of lymph node metastases, demonstrated by an abnormal sequential scan where ^{99}Tc^{m} SbSC had shown the anatomical presence of the ipsilateral IMN and subsequently confirmed by IMN biopsy, is illustrated in *Fig.* 5. No false positive or negative findings were encountered in this small subseries.

One patient, who presented with a large metastatic axillary node mass, had an abnormal internal mammary sequential scan and a computer-assisted tomogram at the level of the second intercostal space (*Fig.* 6) showed a mass in the region of the internal mammary nodes projecting into the right pleural space.

Lymph node radioassay

Radioassay studies of nodes removed soon after IMN scanning using ^{99}Tc^{m} SnP confirmed that normal internal mammary nodes localized the isotope and that the presence of node metastases suppressed localization (*Table I*). The specific activity of normal lymph node was 866 times greater than that of nearby non-target tissue (pectoral muscle). The specific activity of lymph nodes containing metastases was similar to non-target tissue, confirming the marked suppression of uptake.

Discussion

Internal mammary lymph node imaging enables preoperative study of an important area of regional lymph node drainage in breast cancer inaccessible to clinical examination or lymphography. Lymph node imaging was first described following the observation that interstitially injected colloidal radiogold (^{198}Au) was selectively localized in regional lymph nodes (Sherman and Ter-Pogossian, 1953). This agent carried the serious disadvantage of a high radiation dose at the injection site due to a long half-life and beta-particle emission. The isotope technetium-99^{m}, derived from molybdenum, was introduced (Harper et al., 1965), and with a short half-life and gamma emission it had ideal imaging characteristics. ^{99}Tc^{m} sulphur colloid was utilized for lymph node imaging (Hauser et al., 1969) and subsequently Ege (1976) used the antimony sulphide colloid made by a modification of the method of preparing sulphur colloid (Garzon et al., 1965) which yielded a smaller particle size.

Experimental studies using a transplantable tumour model (Rd/3 rat tumour), which metastasized to the regional lymph nodes, showed that ^{99}Tc^{m} SbSC was not as sensitive an agent in detecting lymph node metastases as ^{99}Tc^{m} SnP (Osborne, Jeyasingh et al., 1978). ^{99}Tc^{m} SnP is not a colloid *in vitro* but forms a microcolloid *in vivo* by chelation with calcium ions (Subramanian et al., 1973).

The results of the clinical studies reported here suggest that ^{99}Tc^{m} SnP is suitable for internal mammary lymph node imaging and can detect internal mammary lymph node metastases. Using this agent alone, 38 per cent of the patients studied had abnormal scans; the expected incidence of internal mammary node metastases for central and inner quadrant tumours is 31 per cent (Handley, 1975). Histopathological study of the internal mammary nodes showed good correlation with the preoperative scans with only one false negative finding. A very high uptake of ^{99}Tc^{m} SnP was observed in a node which contained a subcapsular sinus micrometastasis (*Fig.* 4); marked follicular hyperplasia was also present. The significance of micrometastatic nodal disease is questionable as such cases have been shown to have a similar prognosis to patients with negative nodes (Pickren, 1961; Fisher et al., 1978).

One of the patients in the present study (*Fig.* 2) had a node negative axilla and involvement of the internal mammary chain. Those with the internal mammary chain as the sole site of nodal involvement form about 10 per cent of patients with central and inner quadrant tumours (Handley, 1954). In some patients in whom a contralateral injection was given suppression of IMN uptake was observed, suggesting crossover spread of tumour to the contralateral IMN. Crossover of injected colloids has been observed at the xiphoid and manubrial levels (Ege, 1976) and at post-mortem the spread of tumour to the contralateral IMN chain has been seen (Osborne and Bradley, 1979, unpublished data). These observations may have practical importance in the planning of radiotherapeutic fields.

Measurement of lymph node specific activity of injected ^{99}Tc^{m} SnP by radioassay has shown that normal lymph nodes localized the agent and that the presence of lymph node metastases suppresses this localization. Experimental autoradiographic studies have shown that regional lymph node medullary macrophages appear to take up radiolabelled colloidal agents (Mosley et al., 1978). The question whether the suppressed nodal uptake of radiolabelled colloids in the presence of node metastases is due to tumour replacement of the lymph node, mechanical obstruction or a factor produced by the tumour which suppresses macrophage activity has not yet been answered.

One of the major problems in the interpretation of lymphoscintiscans is that a suppressed or absent uptake could be interpreted as either representing lymph node metastases or an anatomical absence of lymph nodes. Using a model in which partial lymph node replacement by tumour reliably occurred, it was shown that ^{99}Tc^{m} SbSC was taken up to a greater degree than ^{99}Tc^{m} SnP and such nodes could be imaged by sequential scanning using their differential uptake to identify their anatomical presence (Osborne, Jeyasingh et al., 1978). The results of sequential scanning in this series suggest that partially involved lymph nodes could be identified using ^{99}Tc^{m} SbSC (*Fig.* 5). Eight patients with suppressed IMN uptake using ^{99}Tc^{m} SnP showed subsequent uptake using ^{99}Tc^{m} SbSC (*Fig.* 3) and this was confirmed histologically in 2 patients. The presence of total nodal replacement by metastatic tumour might raise a problem as no colloidal agent would be localized by such nodes, but computer-assisted axial tomography may be of value (*Fig.* 6) in identifying enlarged IMN.

A method of detecting internal mammary lymph node metastases will result in an improvement in the local staging of breast cancer and will thereby allow a more rational approach to treatment. Without reference to the internal mammary chain serious errors in nodal staging can occur. Although it is possible routinely to biopsy IMN, this is not always convenient and cannot give the complete picture as such nodes may be small and difficult to find. Biopsy cannot give information about contralateral spread to the opposite IMN chain. With an increasing trend towards less radical surgery such a technique may be the only means of detecting IMN metastases without resort to a separate biopsy procedure.

Internal mammary lymphoscintigraphy can give useful information about the regional lymph node drainage in cancer of the breast and further studies are required to evaluate its accuracy.

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References

EGE G. N. (1976) Internal mammary lymphoscintigraphy. *Radiology* **118**, 101–107.

FISHER B., SLACK N. M. and BROSS I. D. J. (1969) Cancer of the breast: size of neoplasm and prognosis. *Cancer* **24**, 1071–1080.

FISHER E. R., SWAMIDOSS S., LEE C. H. et al. (1978) Detection and significance of occult axillary node metastases in patients with invasive breast cancer. *Cancer* **42**, 2025–2031.

GARZON O. L., PALCOF N. C. and RADICELLA R. (1965) Preparation of 99^{m}-Tc antimony sulphide colloid. *Int. J. Appl. Radiat. Isot.* **16**, 613.

HANDLEY R. S. (1975) Carcinoma of the breast. *Ann. R. Coll. Surg. Engl.* **57**, 59–66.

HANDLEY R. S. and THACKRAY A. C. (1954) Invasion of internal mammary lymph nodes in carcinoma of the breast. *Br. Med. J.* **1**, 61–63.

HARPER P. V., LATHROP K. A., JIMINEZ F. et al. (1965) Technetium 99m as a scanning agent. *Radiology* **85**, 101–108.

HAUSER W., ATKINS H. L. and RICHARDS P. (1969) Lymph node scanning with ^{99}Tc^{m}-sulphur colloid. *Radiology* **92**, 1369–1371.

MOSLEY J. G., AGWUNOBI T. C., SHAMA D. et al. (1978) Regional lymph node phagocytic activity inhibition by mouse and human mammary carcinoma. *Br. J. Surg.* **65**, 370.

OSBORNE M. P., JEWKES R., JEYASINGH K. et al. (1973) Internal mammary lymph node scanning in the staging of breast cancer. *Clin. Oncol.* **4**, 393.

OSBORNE M. P., JEYASINGH K., RICHARDSON V. J. et al. (1978) The detection of lymph node metastases using radio-labelled colloids. *Br. J. Surg.* **65**, 354.

PICKREN J. W. (1961) Significance of occult metastases. *Cancer* **14**, 1266–1271.

ROSSI R. and FERRI O. (1966) La visualizzazione della calona mammaria interna con ^{198}Au. Presentazione di una nuova metodica: la linfoscintigrafia. *Minerva Med.* **57**, 1151–1155.

SCHENCK P. (1966) Scintigraphische Darstellung des parasternalen Lymphsystems. *Strahlentherapie* **130**, 504–508.

SHERMAN A. I. and TER-POGOSSIAN M. (1953) Lymph node concentration of radioactive colloidal gold following interstitial injection. *Cancer* **6**, 1238–1240.

SUBRAMANIAN G., MCAFEE J. G., MEHTER A. et al. (1973) ^{99}T^{m}c-stannous phytate. A new *in vivo* colloid for imaging the reticulo-endothelial system. *J. Nucl. Med.* **14**, 459.

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Granular cell myoblastoma of the breast: a report of 2 cases

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SUMMARY

Two cases of granular cell myoblastoma of the breast are presented occurring in women aged 20 and 22 years. The clinical findings, mammographic and naked eye appearances suggested carcinoma. The difficulties of diagnosis and the pathogenesis of this rare tumour are discussed. A definitive histological diagnosis of an apparently malignant breast lump, particularly in a young woman, is mandatory before proceeding to major surgery.

Case reports

Case 1: A 22-year-old student from Indonesia was referred to the combined breast clinic having noticed a lump in the right breast for 3 years. More recently this had been associated with skin dimpling. There was no family history of breast disease, nor any relevant past history. She had been taking Microgynon for 2 years before attending the clinic. There had been no pregnancies. On examination skin dimpling was noted in the upper outer quadrant of the right breast and beneath the dimpling a hard lump measuring 2 × 2 cm was felt; the lump was not freely mobile. No lymph nodes were palpable in the axilla. Despite the patient's age a diagnosis of probable carcinoma of the breast was made. A mammogram was performed and reported as showing 'a vague density with linear extension to the overlying thickened and dimpled skin. No actual mass seen nor any calcification identified. However, malignancy is very likely.' At excision biopsy the surgeon reported the naked eye appearance to be that of a contracting carcinoma and this was also the opinion of the pathologist. A frozen section was not performed, but urgent paraffin section revealed a granular cell myoblastoma.

Pathology

Macroscopically the tumour was a creamy-white colour and merged imperceptibly into the breast parenchyma. *Microscopically* it showed compact tumour cells separated by a variable degree of fibrous tissue. Foci of breast tissue were present in the substance of the tumour (*Fig.* 1). The tumour cells were typically large and polygonal with a small regular vesicular nucleus and abundant granular cytoplasm which appeared eosinophilic on ordinary H and E stain. The cytoplasmic granules stained positively with PAS for mucopolysaccharide and with Sudan IV for fat. Electron microscope studies performed on formalin-fixed material confirmed the paraffin section findings as shown by the following report:

'The sections show large cells with numerous cytoplasmic granular inclusions of variable electron density and composition, many of which are membrane-bound. The cells are aggregated in discrete islands linked by basement membrane. The nuclei show shallow indentations, peripheral condensation of chromatin and prominent nucleoli.

'Study of the cytoplasmic inclusions at higher magnifications shows that they are of complex morphology and contain electron-dense granular or amorphous material as well as small clear vesicles.

'The ultrastructural appearances are in entire agreement with those in previously described electron microscopical studies of granular cell myoblastoma.'

Case 2: A 20-year-old student was referred with a lump in the upper inner quadrant of the right breast, which was described by the referring physician as fixed to the pectoral muscle, 'almost as though within the muscle itself'. When seen in the clinic muscle fixation was not confirmed, the lump being hard and irregular but mobile, and there were no overlying skin changes. Mammography was not arranged as the clinical impression was of a benign lesion, probably a fibroadenoma. Excision biopsy revealed a 1-cm well-circumscribed spherical nodule, the cut surface of which was homogenously white and hard (*Fig.* 2).

Pathology

Macroscopically this tumour had a fibrous pseudocapsule but was otherwise similar in all respects to the first specimen.

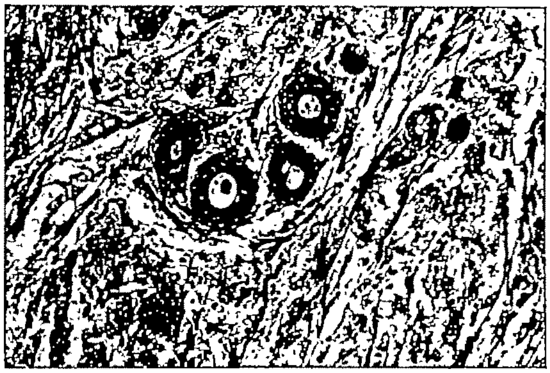

Fig. 1. Presence of breast tissue in the midst of tumour cells (centre). Note the granularity of cells. (PAS. ×100.)

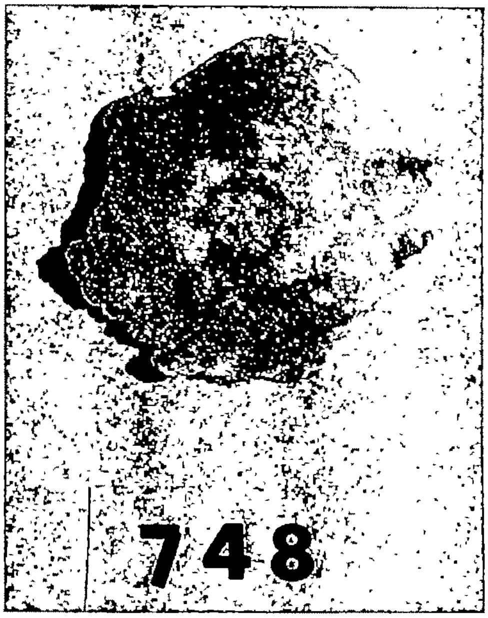

Fig. 2. Gross features of the tumour of *Case* 2. Well-circumscribed spherical mass with regular margins and uniformly homogenous.

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Discussion

Carcinoma of the breast in a woman of 22 is a rare occurrence. Nevertheless the clinical signs in *Case* 1 indicated that carcinoma was the probable diagnosis. Mammography in nulliparous young women is rarely helpful, as the breast disc is too dense to allow of accurate interpretation. However, despite this the radiologist's opinion confirmed the clinical diagnosis of cancer. Only 2 cases of mammographic findings in granular cell myoblastoma have previously been reported (Zuckerman, 1965; Turnbull et al., 1971). Zuckerman demonstrated how this tumour could mimic carcinoma with skin thickening associated with a shadow which had the dendritic properties and dense appearance of a scirrhous cancer. In Turnbull's case the mammogram was reported as benign.

To date less than 50 cases of granular cell myoblastoma of the breast have been reported, none with a correct preoperative diagnosis. Of the 15 cases documented by Mulcare (1968) a diagnosis of cancer was made on 7 occasions (on the basis of either skin or deep fixation), another 7 were diagnosed as fibroadenoma, while one granular cell myoblastoma was found in another part of a breast which had been removed for cancer. The tumour has been reported in patients ranging in age from 21 to 70 years, 3 cases being male (Mulcare, 1968; Leroy et al., 1972; Sussman et al., 1973). In 2 cases mastectomy was performed on the basis of the gross characteristics (Friedman and Hurwitt, 1966).

It has been suggested (Sussman et al., 1973) that needle aspiration is a satisfactory way of establishing the diagnosis. However, this method cannot be recommended, as even in the hands of a proponent of aspiration cytology a benign lesion was all that could be diagnosed, excision biopsy being necessary to reach a definitive diagnosis (Lowhagen and Rubio, 1977).

The place of frozen section in diagnosis of this type of tumour has also caused dispute. Many workers have found it unreliable and indeed dangerous—a diagnosis of carcinoma or fibrosarcoma having been made—with resultant unnecessary mastectomy (Byrne and Dean, 1960; Friedman and Hurwitt, 1966; Mulcare, 1968). Nevertheless, Turnbull et al. (1971) maintained that a reliable diagnosis could be made by this method, and with improved frozen section technique the histopathologist should be capable of diagnosing the lesion.

It is apparent, therefore, that for a tumour presenting in a young woman which is clinically, mammographically and to the naked eye a carcinoma, treatment should initially be by excision biopsy alone until the pathologist's report is available. Provided that a margin of surrounding healthy tissue has been excised (because some of these tumours grow into fascial and muscle planes), no further treatment is indicated should the tumour prove to be a granular cell myoblastoma.

Myoblastomas are rare tumours and were described originally in the tongue by Abrikossoff in 1926. Forty per cent occur in the tongue, but they have also been described in the skin, gastrointestinal tract, respiratory tract, uterus, central and peripheral nervous systems and connective tissue as well as the breast. They are sometimes multiple (Crawford and De Bakey, 1951; Schmidt et al., 1959; Moscovic and Azar, 1967) and not uncommonly regress spontaneously, as do neural tumours. Malignant variants have been described (Ravich et al., 1945; Gamboa, 1955; Krieg, 1962), but these are very rare, and apart from the case reported in 1953 by Crawford and De Bakey in which lesions were noted simultaneously in the lung, liver, coeliac nodes and left breast without an obvious primary tumour, no case of malignant myoblastoma has been described in the breast. The importance of the tumour lies in the fact that it closely mimics breast cancer, both clinically and on naked eye examination.

Various theories have been propounded as to the true nature of the granular cell myoblastoma, whose cellular origin is controversial. The term myoblastoma was coined by early writers because of the tumour's association with voluntary muscle, e.g. the tongue (Svejda and Horn, 1958; Fisher and Wechshler, 1962). Aparicio and Lumsden in 1969, using histochemical and electron microscopy studies, concluded that myoblastoma were 'slow growing new growths whose cells have leiomyogenic affinities perhaps peculiar to special skeletal muscle structures'. However, in 1971, as a result of electron microscopy and cytochemical studies of seven typical granular cell myoblastomas (one of which was in the breast), Sobel et al. (1971), while stating that a definite conclusion about the nature of granular cell myoblastomas was not possible, postulated that the myoblastoma was a tumour-like lesion of Schwann cell origin which represented a reactive cellular response or, more likely, a true neoplasm. In later work Sobel concluded that the tumour was derived from an undifferentiated mesenchymal cell that may also be the precursor of the schwannoma, thus making the schwannoma and myoblastoma related to each other as well as to the fibroblast (Sobel et al., 1973).

Light microscopy is quite adequate to establish a diagnosis, which may be reinforced by cytochemical stains. Electron microscopy studies are only required as research tools to study the histogenesis of the tumour.

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References

ABRIKOSSOFF A. (1926) Über Myome, ausgehend von der quergestreiften willkurlichen Musculatur. *Virchows Arch. Pathol. Anat.* **260**, 215–233.

APARICIO S. R. and LUMSDEN C. E. (1969) Light and electron microscope studies on the granular cell myoblastoma of the tongue. *J. Pathol.* **97**, 339–355.

BYRNE J. J. and DEAN M. A. (1960) Granular cell myoblastoma of the breast. *Am. J. Surg.* **100**, 98–102.

CRAWFORD E. S. and DE BAKEY M. E. (1953) Granular cell myoblastoma. Two unusual cases. *Cancer* **6**, 786–789.

FISHER E. R. and WECHSHLER H. (1962) Granular cell myoblastoma—a misnomer. Electron microscopic and histochemical evidence concerning its Schwann cell derivation and nature (granular cell schwannoma). *Cancer* **15**, 936–954.

FRIEDMAN R. M. and HURWITT E. S. (1966) Granular cell myoblastoma of the breast. *Am. J. Surg.* **112**, 76–79.

GAMBOA L. G. (1955) Malignant granular cell myoblastoma. *Arch. Pathol.* **60**, 663–668.

KRIEG A. F. (1962) Malignant granular cell myoblastoma. A case report. *Arch. Pathol.* **74**, 251–256.

LEROY J. P., BALOUET G. and SALEUN J. P. (1972) Tumeurs à cellules granuleuses. *Arch. Anat. Pathol.* **20**, 157–162.

LOWHAGEN T. and RUBIO A. (1977) The cytology of granular cell myoblastoma. Report of a case. *Acta Cytol.* **21**, 314–315.

MOSCOVIC E. A. and AZAR H. A. (1967) Multiple granular cell tumours ('myoblastomas'). Case report with electron microscopic observations and review of the literature. *Cancer* **20**, 2032–2047.

MULCARE R. (1968) Granular cell myoblastoma of the breast. *Ann. Surg.* **168**, 262–268.

RAVICH A., STOUT A. P. and RAVICH R. A. (1945) Malignant granular cell myoblastoma involving the urinary bladder. *Ann. Surg.* **121**, 361–372.

SCHMIDT E., AMBLER J. and WROTH R. (1959) Multiple granular cell myoblastomas. *Maryland Med. J.* **8**, 287–290.

SOBEL H. J., MARQUET E., AVRIN E. et al. (1971) Granular cell myoblastoma. An electron microscopic and cytochemical study illustrating the genesis of granules and aging of myoblastoma cells. *Am. J. Pathol.* **65**, 59–78.

SOBEL H. J., SCHWARZ R. and MARQUET E. (1973) Light and electron microscope study of the origin of granular cell myoblastoma. *J. Pathol.* **109**, 101–111.

SUSSMAN E. B., HAJDU S. I. and GRAY G. F. (1973) Granular cell myoblastoma of the breast. *Am. J. Surg.* **126**, 669–670.

SVEJDA J. and HORN V. (1958) A disseminated granular cell pseudotumour, so called metastasising granular-cell myoblastoma. *J. Pathol. Bacteriol.* **76**, 343–348.

TURNBULL A. D., HUVOS A. G., ASHIKARI R. et al. (1971) Granular cell myoblastoma of breast. *NY State J. Med.* **71**, 436–438.

ZUCKERMAN H. C. (1965) Mammography in the diagnosis of cancer of the breast. *Prog. Clin. Cancer* **1**, 185–212.

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Salmonellosis associated with late rupture of an aortofemoral bypass graft

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SUMMARY
Salmonella infection is a rare cause of rupture of the atherosclerotic abdominal aneurysm. A case never previously reported is presented in which salmonella infection occurred involving an aortofemoral bypass graft which had been inserted 10 years previously. The infection caused a leak in the region of the graft which presented as a haematoma in the thigh.

LARGE vessels such as the aorta are normally very resistant to infection. This resistance, however, is impaired in the presence of vascular anomalies and other arterial lesions such as atherosclerosis and syphilitic arteritis (Ten Eyck and Wellman, 1959). There are 23 reports in the literature (Kanwar et al., 1974; Porschen et al., 1977) of salmonella infections occurring in patients with atherosclerotic abdominal aortic aneurysms. Salmonella infection, however, has never previously been reported occurring in a synthetic vascular graft.

Case report

R. R., a 63-year-old male, had been fit and well following a bilateral aortofemoral bypass graft and sympathectomy in 1968. He presented to the Royal Hobart Hospital on 22 May 1978 complaining of pain in his right loin and right hypochondrium. The symptoms rapidly improved and a cholecystogram confirmed the presence of gallstones. He was allowed home but was readmitted the next week complaining of pain in the left iliac fossa with some radiation to the groin. His doctor reported that the patient had had a swinging pyrexia and had lost 2 stone (13 kg) in weight over a period of about 3 weeks.

On admission the adductor region of the left thigh was markedly swollen and tender. The hip remained flexed at about 45° and there was a swinging temperature ranging from 36·9 °C to 39 °C. Blood cultures grew *Salmonella choleraesuis* (variant Kuzendorf), this identification being confirmed by the Salmonella Reference Laboratory (Institute of Medical and Veterinary Science, Adelaide). The organism was sensitive to chloramphenicol, ampicillin and gentamicin. No salmonellae were isolated from stool and urine cultures despite multiple cultures. Initial X-ray of the spine showed mild degenerative changes only, although later tomograms did suggest a defect in the upper anterior cortex of L1. Barium meal, gastroscopy, bone scan and ultrasound did not aid the diagnosis.

The patient was treated with ampicillin and then chloramphenicol and he clinically started to improve, although he continued with a low grade pyrexia and the left thigh remained swollen. Three weeks after admission the swelling of the thigh had become fluctuant and a further fluctuant area was present just medial to the anterior superior iliac spine. Between these two areas cross-fluctuation was present.

At operation (14 July 1978) a needle was inserted into the thigh and blood aspirated. It was decided then to proceed with a laparotomy at which a large pulsating haematoma on the left side of the pelvis was identified. Further examination revealed a leak in the region of the proximal end of the existing aortofemoral graft. The proximal end of the graft was therefore excised and a large defect was found involving the adjacent posterior wall of the aorta. The defect extended between the two lumbar vertebrae (*Fig.* 1) and the intervertebral disc had completely disappeared. A sleeve graft of

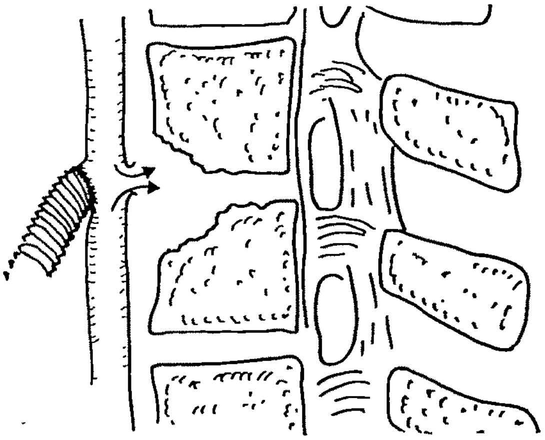

Fig. 1.

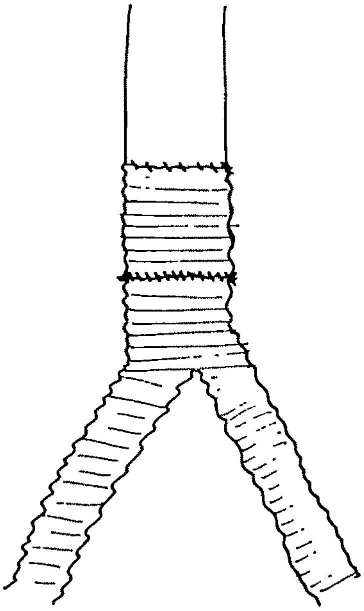

Fig. 2.

Dacron was then inserted between the proximal aorta and the distal part of the existing bypass graft (*Fig.* 2). *S. choleraesuis* was isolated from the haematoma aspirate, portions of graft and the excised aortic wall. The patient was therefore commenced postoperatively on 12 g of ampicillin with the subsequent addition of gentamicin 80 mg t.d.s. when the

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Table I: A SUMMARY OF THE MAJOR FEATURES OF SALMONELLA ENDOVASCULITIS ASSOCIATED WITH AORTIC ANEURYSM (INCLUDING THE PRESENT CASE)

	No.	%
Causative serotype		
S. choleraesuis	8	33
S. typhimurium	7	29
Others	9	38
Sites of positive culture		
Blood	20	83
Stool	12	50
Urine	9	38
Involvement of lumbar vertebrae	9	38
Diagnosed only at post-mortem	14	58
Surgical repair undertaken	10	42
Long term survivors	4	17

Total number of reported cases = 24.

drainage fluid continued to show a moderate growth of *S. choleraesuis*. This growth gradually lessened over the next 2 weeks as shown by daily culture until by 6 August 1978 three consecutive negative specimens of drainage fluid had been obtained and the drains were then removed. The patient made an excellent postoperative recovery and 4 months later remains well. He is still maintained on ampicillin 500 mg q.i.d. 6 months after operation.

Discussion

There are 23 reports available in the literature concerning salmonella infection causing rupture of an atherosclerotic abdominal aneurysm. Zak has previously emphasized the importance of recognizing this entity in patients known to have arterial aneurysms who subsequently develop salmonella infections, as well as in patients with salmonellosis who die in irreversible shock (Zak et al., 1958).

This case is the first of its kind in which infection has occurred in association with a prosthetic Dacron graft. The commonest salmonella affecting the Australian population, according to the Australian Communicable Diseases Intelligence 1978 (nos. 18, 3 and 8), is *S. typhimurium*, with no overall preponderance of any other serotype. At our own hospital from January 1977 to November 1978 65 cases of salmonellosis have been identified. Of these, 48 (74 per cent) were cases of *S. typhimurium*. Our patient was the only case of *S. choleraesuis* identified during this period. This strain, although it is not a common cause of salmonella infection, accounts for 8 out of the 23 reported cases of aorto-endovasculitis, i.e. an incidence of 33 per cent.

If invasion from the gastrointestinal tract occurs, septicaemia, multiple abscess, osteomyelitis and aortitis can develop. Patients especially at risk of developing systemic disease are those with sickle cell anaemia (Hand and King, 1978) or gastrointestinal carcinoma (Youmans et al., 1978).

There are two possible mechanisms which could have operated in our cases. Infection may have developed in the arterial wall following septicaemia with subsequent rupture and vertebral erosion. Alternatively, there may have been a direct extension from the adjoining lumbar vertebrae following a lumbar osteomyelitis causing rupture of the arterial wall. The symptom sequence, however, suggests the former.

On reviewing the literature, the commonest symptoms of this condition are fever, abdominal pain and back pain. Positive blood culture was present in 19 cases and there was an associated osteomyelitis of the lumbar vertebrae in 8 of these. Including our own, 24 cases have been reported (*Table I*): 14 of them were diagnosed at post-mortem; 9 patients underwent an attempted surgical repair, but only 4 of the patients have survived surgery. To the best of our knowledge this is the first reported case involving a synthetic graft. This case is presented because it emphasizes several important points. In only 10 of the 24 reported patients was the cause diagnosed before death. *S. choleraesuis* is the salmonella most often associated with infection of diseased blood vessels and should be suspected in patients with known arterial disease who become shocked after salmonella infection, especially if this shock is unresponsive to conventional measures.

Finally, because of the infrequency of this disease, there are no established guidelines to indicate how long the patient should be maintained on ampicillin. Experience with treatment of carriers has shown successful eradication with 3 months' therapy (Garrard and Lambert, 1973). However, the well-known persistence of these organisms in the tissues with subsequent relapse and the presence of a synthetic graft makes the decision about when to cease medication difficult.

References

GARRARD L. P., LAMBERT H. P. and O'GRADY F. (1973). *Antibiotics and Chemotherapy*, p. 367.

HAND W. L. and KING N. L. (1978) Serum opsonization of salmonella in sickle cell anaemia. *Am. J. Med.* 64, 388–395.

KANWAR Y. S., MALHOTRA U., BURTON R. H. et al. (1974) Salmonellosis associated with abdominal aortic aneurysm. *Arch. Intern. Med.* 134, 1095–1098.

PORSCHEN R. K., HALE D. and GOODMAN Z. (1977) Misdiagnosed salmonella septicaemia and endarteritis due to a lactose fermenting strain. *Am. J. Clin. Pathol.* 68, 415–419.

TEN EYCK F. W. and WELLMAN W. E. (1959) Salmonellosis associated with abdominal aortic aneurysm and edema of lower extremities. A case report. *Postgrad. Med. J.* 26, 334–339.

YOUMANS G. P., PATERSON P. Y. and SOMMERS H. M. (1975) *The Biologic and Clinical Basis of Infectious Diseases*, p. 4-3.

ZAK F. G., STRAUSS L. and SAPHORA I. (1958) Rupture of diseased large arteries in the course of enterobacterial (Salmonella) infections. *N. Engl. J. Med.* 258, 824–828.

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Emergency treatment of variceal haemorrhage*

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SUMMARY

For the initial control of haemorrhage from oesophageal varices, two methods of vasopressin administration have been compared—the conventional bolus of 20 units and a low dose infusion of 0·4 units per minute.

Twenty patients bleeding from oesophageal varices, confirmed by endoscopy, were allocated into either treatment group (10 in each). Vasopressin infusion stopped bleeding in 86 per cent of the episodes in contrast to 12·5 per cent ($P<0{\cdot}01$) with bolus doses. Balloon tamponade with a Sengstaken-Blakemore tube was used to control bleeding in only 2 episodes in patients on infusion and in 10 episodes in patients on bolus doses of vasopressin ($P<0{\cdot}05$). Our study confirms that low dose vasopressin infusion is more effective in controlling bleeding from oesophageal varices than conventional bolus doses.

In cirrhotic patients, bleeding from oesophageal varices is a critical event. About half of those patients admitted to hospital die (Rothwell-Jackson and Hunt, 1971; George et al., 1973). The rapid control of massive bleeding constitutes the major initial challenge in the emergency treatment of such patients. Despite encouraging reports (Orloff et al., 1975), emergency portasystemic shunts are followed by an unacceptably high morbidity and mortality rate. Direct occlusion of the varices by operations such as oesophageal or gastric transection carries a considerable postoperative mortality (in our hands 50 per cent overall and 90 per cent in Child's (1964) group C). Therefore, we, with others, are seeking to develop simpler, non-operative measures to control bleeding from varices.

The initial treatment of these patients is usually the intravenous administration of vasopressin. We decided to determine whether *continuous infusion* was more effective than the more conventional repeated *bolus* injections.

Patients and methods

Over a 2-year period (June 1976 to May 1978), 20 patients who were admitted to the Professorial Unit, Liverpool Royal Infirmary, with active bleeding from varices were considered suitable for vasopressin treatment. All these patients were emergency admissions, either coming directly into our unit or being transferred from other hospitals after massive haemorrhages. Bleeding from varices was confirmed by endoscopy and/or barium studies within 24 h of admission.

During the first 12 months (June 1976 to May 1977) of this study all patients were treated with repeated bolus intravenous injections of vasopressin (bolus group, $n = 10$). Doses of 20 units diluted in 100 ml dextrose 5 per cent w/v solution were injected over a period of 20 min and repeated at intervals of 2–4 h until the bleeding stopped. In the second year (June 1977 to May 1978) the patients were treated with a continuous infusion of vasopressin (infusion group, $n = 10$). Vasopressin (200 units) was diluted in 500 ml dextrose 5 per cent w/v solution and infused at a rate of 0·4 units/min. This low rate of infusion was achieved using an IVAC pump. When bleeding was controlled and vital signs stabilized, infusion was gradually decreased and stopped within the next 12 h.

The initial general resuscitation of all patients with bleeding varices admitted to our unit is standard and includes replacement of blood, fluid and electrolytes, the correction of coagulation defects and continuous nasogastric aspiration (Shields, 1977). All patients were monitored for pulse rate, blood pressure and central venous pressure changes and with continuous electrocardiography.

There were 16 episodes of bleeding treated with bolus vasopressin and 15 with continuous infusion. Treatment was regarded as successful if bleeding was stopped and no further haemorrhage occurred within 24 h of cessation of vasopressin. If bleeding persisted or recurred within 24 h, our policy was to use balloon tamponade with a Sengstaken-Blakemore tube to control haemorrhage. Hence, another index of success or failure of vasopressin treatment was the frequency of balloon tamponade.

Results

Comparability of groups

The two groups of patients were well matched for numbers, age, sex (*Table I*), assessment of liver function (Child, 1964) and the aetiology of cirrhosis (*Table II*). The diagnosis of cirrhosis was confirmed on subsequent histology. The majority of the patients had alcoholic cirrhosis—7 of the 10 patients in the bolus group and 9 of the 10 in the infusion group. One patient in each group had primary biliary cirrhosis, one patient in the bolus group had schistosomiasis and another portal vein thrombosis.

Table I: AGE AND SEX DISTRIBUTION IN BOTH GROUPS

Vasopressin	Mean age (yr)	Males	Females
Bolus ($n = 10$)	50·5±3·6	9	1
Infusion ($n = 10$)	53·8±2·4	8	2

Table II: CLINICAL STAGING AND AETIOLOGY OF CIRRHOSIS

	Child's classification			Aetiology of cirrhosis		
	A	B	C	Alcoholic	Primary biliary	Other
Bolus	1	5	4	7	1	2*
Infusion	—	6	4	9	1	—

* Portal vein thrombosis and schistosomiasis.

Control of bleeding

Bleeding was controlled in only 2 of the 16 episodes (12·5 per cent) when vasopressin was given in the conventional bolus doses. In contrast, using a continuous infusion of vasopressin, bleeding was stopped in 13 of the 15 episodes (86 per cent). Balloon tamponade was used on 10 occasions in 8 patients in the bolus group (*Fig.* 1*a*) and in only 1 patient (on 2 occasions) in the infusion group (*Fig.* 1*b*) ($P<0{\cdot}05\chi^2$). Emergency operations (oesophageal or gastric transection) were carried out in 7 patients to control bleeding: 6 in the bolus group and 1 in the infusion

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* Paper presented at the Annual Meeting of the Association of Surgeons, Norwich, April 1979.

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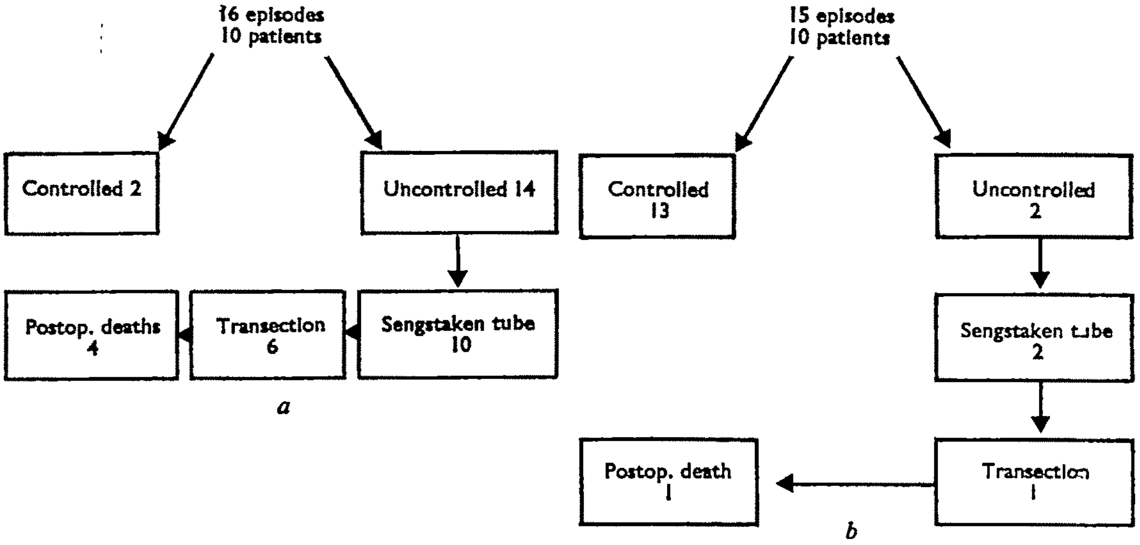

Fig. 1. Outcome of patients in (*a*) the bolus group and (*b*) the infusion group.

group. In 3 patients in the infusion group portasystemic shunt was performed as an elective procedure after necessary investigations and preparations.

Mortality

Nine patients died (45 per cent)—5 after operations, 4 due to liver failure and 1 due to massive haemorrhage (*Table III*). Three patients were found to have malignant disease—1 hepatoma in each group and 1 carcinoma of the bronchus for which no operation was carried out. One patient died after massive haemorrhage in spite of strenuous efforts at resuscitation.

Blood tranfusion requirements (*Table III*)

The amount of blood transfused per episode, estimated as units, was not significantly different between the two groups: 4·7 (±1·8 s.d.) in the bolus group and 3·8 (±0·6 s.d.) in the infusion group. However, it should be noted that many of our patients were referred from other hospitals where variable quantities of blood had been transfused so that comparison of the groups was difficult.

Discussion

Vasopressin is a powerful vasoconstrictor and its role in the management and control of bleeding oesophageal varices has been, and is still, under investigation. The report of Kehne et al. (1956) of successful control of variceal haemorrhage with intermittent and repeated intravenous injections of vasopressin is the basis of current conventional treatment. However the initial promise of this treatment was not realized, as recurrent bleeding on stopping the drug was common and systemic effects, such as coronary insufficiency, decreased cardiac output and in some cases peripheral vascular collapse, were reported (Wexler, 1977). A tachyphylactic effect with diminished vascular response was also seen with repeated bolus injection. Nusbaum and Conn (1976) showed that systemic side effects could be abolished by infusing vasopressin directly into the superior mesenteric artery. Intra-arterial vasopressin infused in low doses of 0·2 units/min reduced portal venous pressure by 50 per cent and superior mesenteric artery flow by 60 per cent.

Table III: BLOOD TRANSFUSED AND POSTOPERATIVE MORTALITY

	Blood transfused (units)	Postop. deaths
Bolus	4·7 (±1·8)	4
Infusion	3·8 (±0·6)	1

In a prospective controlled trial, Conn and his colleagues (1975), in a comparison of intra-arterial infusions and conventional bolus treatment, reported that the former was more effective in controlling haemorrhage. They also showed that, with intra-arterial infusions, blood transfusion requirements were reduced. However, the overall morbidity and mortality in the two groups and long term survival were not significantly different. In animal studies Barr et al. (1975) found no significant difference in the haemodynamic effects of selective superior mesenteric artery and intravenous infusions of vasopressin in similar concentrations. These findings were further substantiated by Kerr and colleagues (1978). A recent clinical study by Johnson et al. (1977) confirmed that intravenous infusion of vasopressin was as effective as an intra-arterial infusion of the same dose.

Our study compared the conventional bolus injections with intravenous infusion as the latter eliminates the technical problems of selective superior mesenteric artery catheterization. Our results clearly show that simple intravenous infusion of vasopressin in low doses is more effective than conventional repeated bolus doses. The biological half-life of vasopressin is 20–25 min in man (Bauman and Dingman, 1976) and the therapeutic half-life is less than 5 min (Williams, 1978). Therefore, bolus injection can at best produce only a brief reduction in portal venous pressure whilst, in contrast, a continuous infusion probably produces prolonged sustained effects.

Our management of bleeding oesophageal varices was staged: vasopressin (stage I) followed by balloon tamponade (stage II) and finally, if required, emergency operation (stage III). Progression from one stage to another indicated failure of a previous stage. In the infusion group, only one patient reached stage III, whilst in the bolus group, 8 reached stage II and 6 stage III. In these last 6 patients operative disconnection of the gastro-oesophageal varices from the portal circulation was carried out in an attempt to stop bleeding and save life.

Surgery, in such emergency circumstances, carries a high mortality (5 out of 7 in the present study) and all efforts should be made to avoid operations. Other less traumatic procedures such as sclerotherapy either directly into the varices (Terblanche, 1979) or via coronary vein catheterization (Lunderquist and Vang, 1974) could be considered. If bleeding is stopped at stage I, the patient can be assessed clinically, biochemically and radiologically and a decision made as regards future treatment. We feel that if there is good liver function and a patent portal or superior mesenteric vein, an urgent shunt gives the best prognosis.

The main criticism of our study is that the comparison of the two treatment schedules was not by a random controlled trial. Whilst it is probable that the patient population may differ from year to year, our two groups seem to be matched as regards episodes of bleeding, age, aetiology of cirrhosis and Child's classification of liver function. Recently in this context, the significance of controlled trials has been questioned, and it has been suggested that 'in conditions with a high mortality historical controls may be entirely acceptable' (Editorial, 1979).

References

BARR J. W., LAKIN R. C. and ROSCH J. (1975) Similarity of arterial and intravenous vasopressin on portal and systemic haemodynamics. *Gastroenterology* **69**, 13–19.

BAUMAN G. and DINGMAN J. F. (1976) Distribution, blood transport and degradation of antidiuretic hormone in man. *J. Clin. Invest.* **57**, 1109–1116.

CHILD C. G. (1964) *Major Problems in Clinical Surgery, Vol. 1: The Liver and Portal Hypertension.* Philadelphia, Saunders, pp. 1, 49.

CONN H. O., TAMSBY G. R., STORER L. H. et al. (1975) Intra-arterial vasopressin in the treatment of upper gastro-intestinal haemorrhage. *Gastroenterology* **68**, 211–221.

EDITORIAL (1979) Controlled trials—planned deception. *Lancet* **1**, 534–535.

GEORGE P., BROWN C., RIDGWAY G. et al. (1973) Emergency oesophageal transection in uncontrolled variceal haemorrhage. *Br. J. Surg.* **60**, 635–640.

JOHNSON W. C., WILDICH W. C., ANSELL J. E. et al. (1977) Control of bleeding varices by vasopressin. *Ann. Surg.* **186**, 369–376.

KEHNE J. H., HUGHES F. A. and GOURPERTZ M. L. (1956) The use of surgical pituitrin in the control of oesophageal varix bleeding. *Surgery* **39**, 917–925.

KERR J. C., HOBSON R. W., SEELIG R. I. et al. (1978) Vasopressin: route of administration and effects on canine hepatic and superior mesenteric arterial blood flows. *Ann. Surg.* **187**, 137–142.

LUNDERQUIST A. and VANG J. (1974) Transhepatic catheterisation and obliteration of the coronary vein in patients with portal hypertension and oesophageal varices. *N. Engl. J. Med.* **291**, 646–650.

NUSBAUM M. and CONN H. O. (1975) Arterial vasopressin infusion: science or seance? *Gastroenterology* **69**, 263–267.

ORLOFF M. J., CHARTERS A. C., CHANDER J. G. et al. (1975) Portacaval shunt as emergency procedure in unselected patients with alcoholic cirrhosis. *Surg. Gynecol. Obstet.* **141**, 59–68.

ROTHWELL-JACKSON R. L. and HUNT A. H. (1971) The results obtained with emergency surgery in the treatment of persistent haemorrhage from gastro-oesophageal varices in the cirrhotic patient. *Br. J. Surg.* **58**, 205–215.

SHIELDS R. (1977) The management of portal hypertension and bleeding oesophageal varices. *Br. J. Hosp. Med.* **18**, 126–143.

TERBLANCHE J., NORTHOVER J. M. A., BOONMAN P. et al. (1979) A prospective evaluation of injection sclerotherapy in the treatment of acute bleeding from oesophageal varices. *Surgery* **85**, 239–245.

WEXLER M. J. (1977) Benefits of vasopressin in gastro-intestinal haemorrhage. *Can. J. Surg.* **20**, 310–313.

WILLIAMS R. (1978) Advances in the investigation and treatment of liver disease. *Practitioner* **221**, 523–530.

Br. J. Surg. Vol. 66 (1979) 827–828

Haematemesis in infantile hypertrophic pyloric stenosis: the source of the bleeding

LEWIS SPITZ AND GILLIAN BATCUP*

SUMMARY

Thirteen infants with haematemesis associated with hypertrophic pyloric stenosis were investigated in order to elucidate the source of bleeding. All 13 patients showed endoscopic evidence of oesophagitis, moderate in 4 and severe in 9. No significant gastric mucosal lesion was found. It was concluded that the site of the haemorrhage was the oesophageal mucosa in all 13 infants. Eleven of the patients experienced troublesome postoperative vomiting.

THE reported incidence of haematemesis, as defined by the presence of streaks of red blood or 'coffee-ground' material in the vomitus, in infants with hypertrophic pyloric stenosis varies from 0·9 to 17·5 per cent (*Table I*). The source of the haemorrhage has been assumed by most authors to be acute or chronic gastritis secondary to gastric stasis due to the pyloric obstruction (Swenson, 1969; Benson, 1971; Nixon, 1976; Cook and Rickham, 1978). Dodge (1975a) noted the necropsy finding of superficial ulceration of the oesophagus in 2 infants with pyloric stenosis in whom there was a history of bloodstained vomiting.

This study was undertaken in order to establish the site of the haemorrhage in those infants with hypertrophic pyloric stenosis who presented with a history of haematemesis or who were noted to vomit blood during preoperative preparation.

Table I: INCIDENCE OF HAEMATEMESIS IN PATIENTS WITH INFANTILE PYLORIC STENOSIS

Series	Incidence of haematemesis (%)
Terezis et al. (1959)	0·9
Miller and Friesen (1956)	2·3
Rienlander and Swenson (1952)	4
Malberg (1949)	8
Pollock et al. (1957)	13
Dodge (1975)	17·5
Cook and Rickham (1978)	17–18

Patients and methods

Of a total of 78 infants with hypertrophic pyloric stenosis treated at The Children's Hospital, Sheffield, during a 3½-year period (August 1975 to January 1979), 13 (16·7 per cent) were noted preoperatively to have haematemesis.

The routine preoperative preparation of all the infants with pyloric stenosis consisted of correction of fluid and electrolyte and acid–base imbalances, where appropriate, and gentle saline nasogastric lavage to evacuate the stomach of retained milk curds. The infants were operated upon under endotracheal anaesthesia and under the same anaesthetic an endoscopic examination of the oesophagus and stomach was carried out using an Olympus Paediatric Oesophagofibrescope, Model EP Type PA (maximum external diameter 7·2 mm) in order to ascertain the site of haemorrhage. In 9 patients a random mucosal punch biopsy was taken from the greater curvature of the stomach at a point approximately two-thirds of the distance from the gastro-oesophageal junction to the pyloric sphincter. No complications from the endoscopic procedures were encountered.

Findings on endoscopy

Endoscopically four grades of oesophageal mucosal change were recognized: grade 0, normal appearance; grade I, mild erythema of the distal third of the oesophagus only; grade II, an erythematous and friable mucous membrane; grade III, superficial ulceration of the mucosa of the distal oesophagus, in addition erythema and friability.

Of the 13 infants manifesting haematemesis, 4 were classified as having grade II oesophageal changes and 9 as having grade III lesions. Scattered punctate haemorrhages were seen in the gastric mucosal surface in 6 infants, but there was no evidence endoscopically of a diffuse mucosal lesion or of an active bleeding site in the stomach.

Histopathological findings

This formed part of a study in which gastric mucosal biopsies from 35 infants with hypertrophic pyloric stenosis were compared with 33 post-mortem sections of 'normal' stomach from age-matched control cases selected to exclude any clinical history of diarrhoea or vomiting except as a terminal event (Batcup and Spitz, 1979).

None of these 35 biopsies showed mucosal erosions or an increased inflammatory cell infiltration within the lamina propria. There was thus no histological evidence of a diffuse gastritis, although examination of such a small sample could not exclude focal erosions elsewhere in the stomach.

Although three of the biopsies from infants with haematemesis showed fresh haemorrhage into the lamina propria, similar findings were recorded in a further 15 biopsies from cases with no such history, and also in 12 of the control group. In addition, no significant mucosal deposition of haemosiderin was noted. These findings suggest that there is no direct relationship between gastric mucosal haemorrhage and the presence or absence of haematemesis.

Discussion

The results of this study of 13 infants with hypertrophic pyloric stenosis presenting with haematemesis show, contrary to general opinion, that the source of the bleeding is the oesophageal rather than the gastric mucosa. As bilious vomiting is virtually unknown in pyloric stenosis (Benson, 1969; Dodge, 1975b; Cook and Rickham, 1979) it can be safely assumed that the pathological changes seen in the oesophagus are secondary to acid–pepsin reflux.

Incompetence of the lower oesophageal sphincter has been previously recorded by many authors, notably Forshall (1955) and Roviralta (1967). Pellerin et al. (1974) demonstrated reflux radiologically in 13 per cent of 627 infants with pyloric stenosis. In an unselected consecutive study of 72 infants with pyloric stenosis the incidence of oesophagitis was found on endoscopic examination to be as high as 30 per cent (Spitz, 1979).

Punctate haemorrhages in the mucosal surface of the stomach were noted in 6 of the 13 infants. No active bleeding site in the stomach could be seen in any of these patients and the presence of punctate haemorrhages did not correlate with the severity of the haematemesis. The role of the nasogastric tube in the pathogenesis of the haemorrhages is unknown, but it is of interest to note that similar lesions were noted in 20 per cent of infants with uncomplicated pyloric stenosis. This observation, together with the results of the histopathological study of mucosal punch biopsies, would tend to support the view that gastric mucosal lesions are not normally associated with pyloric stenosis. Frank ulceration of the stomach has, however, been reported in an infant with pyloric stenosis (Kelsey et al., 1968).

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The clinical significance of the haematemesis in pyloric stenosis was stressed by Haberer as long ago as 1932. He noted that infants showing blood in their vomitus preoperatively were more likely to experience troublesome postoperative vomiting. This observation was substantiated in this series of 13 patients, 11 of whom experienced significant vomiting in the postoperative period.

References

BATCUP G and SPITZ L. (1979) A histopathological study of gastric mucosal biopsies in infantile hypertrophic pyloric stenosis. *J. Clin. Pathol.* **32**, 625–628.

BENSON C. D. (1969) Infantile hypertrophic pyloric stenosis. In: MUSTARD W. T., RAVITCH M. M., SNYDER W. H. et al. (ed.) *Pediatric Surgery*, 2nd ed. Chicago, Year Book, pp. 818–822.

BENSON C. D. (1971) Infantile pyloric stenosis. Historical aspects and current surgical concepts. *Prog. Pediatr. Surg.* **1**, 63–88.

COOK R. C. M. and RICKHAM P. P. (1978) Gastric outlet obstructions. In: RICKHAM P. P., LISTER J. and IRVING I. M. (ed.) *Neonatal Surgery*, 2nd ed. London, Butterworths, pp. 335–351.

DODGE J. A. (1975a) Infantile hypertrophic pyloric stenosis in Belfast, 1957–1969. *Arch. Dis. Child.* **50**, 171–178.

DODGE J. A. (1975b) The stomach. In: C. M. ANDERSON and V. BURKE (ed.) *Paediatric Gastroenterology.* Oxford, Blackwell Scientific, pp. 81–123.

FORSHALL I. (1955) The cardio-oesophageal syndrome in childhood. *Arch. Dis. Child.* **30**, 46–54.

KELSEY D., STAYMAN J. W., MCLAUGHLIN E. D. et al. (1968) Massive bleeding in a newborn infant from a gastric ulcer associated with hypertrophic pyloric stenosis. *Surgery* **64**, 979–982.

MALBERG N. (1949) Hypertrophic pyloric stenosis. *Acta Pediatr. Scand.* **38**, 472–483.

MILLER D. R. and FRIESEN S. R. (1956) Hypertrophic pyloric stenosis: a clinical analysis of 87 cases with special reference to etiological factors. *Am. Surg.* **22**, 108–117.

NIXON H. H. (1976) In: NIXON H. H. and O'CONNELL B. (ed.) *The Essentials of Paediatric Surgery*, 3rd ed. London, Heinemann, pp. 70–77.

PELLERIN D., BERTIN P. and TOVAR J. A. (1974) Reflux gastro-œsophagien et sténose hypertrophique du pylore. *Ann. Chir. Infant.* **15**, 7–14.

POLLOCK W. F., NORRIS W. J. and GORDON H. E. (1957) The management of hypertrophic pyloric stenosis at the Los Angeles Children's Hospital. A review of 1422 cases. *Am. J. Surg.* **94**, 335–348.

RIENLANDER H. F. and SWENSON O. (1952) The diagnosis and management of congenital hypertrophic pyloric stenosis. *J. Pediatr.* **41**, 314–319.

ROVIRALTA E. (1967) Le syndrome phréno-pylorique. In: *Hernies et Ecopies Partielles de l'Estomac chez l'Enfant.* Paris, Masson.

SPITZ L. (1979) Vomiting after pyloromyotomy for infantile pyloric stenosis. *Arch. Dis. Child.* (In the press.)

SWENSON O. (1969) In: SWENSON O. (ed.) *Pediatric Surgery.* New York, Meredith, pp. 596–605.

TEREZIS N. L., SIEBER W. K. and KIESEWETTER W. B. (1959) The prognostic significance of electrolyte and weight studies in congenital hypertrophic pyloric stenosis. *Surg. Gynecol. Obstet.* **109**, 482–486.

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Br. J. Surg. Vol. 66 (1979) 829–830

Correspondence

Phlegmasia caerulea dolens

Sir

I was disturbed by the conclusion to which the authors of the paper 'The role of thrombolytic therapy in the management of phlegmasia caerulea dolens' (M. S. Elliot et al., *Br. J. Surg.* 66, 422–424) came concerning the effectiveness of thrombolytic therapy in this condition. In both cases the post-treatment venogram showed occlusion of the venous tree, and it would seem to me that the authors have not demonstrated that thrombolytic therapy *per se* has been responsible for the improvement. There can be no doubt that there was improvement in these patients, but we are all aware of the development of venous collaterals in such cases even in the absence of treatment.

I do not therefore believe there are necessarily grounds for attributing this success to the use of streptokinase.

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Sir

Miss Mansfield has raised a valid argument which we cannot entirely refute as pre-treatment phlebography was not possible for technical reasons in either of the patients described. Both patients exhibited residual thrombosis of the deep venous system at phlebography 14 days after treatment. In *Case* 1 this involved the calf, popliteal and superficial femoral vein but with iliac patency and almost complete superficial vein patency. In *Case* 2 there was persistent iliofemoral thrombus but with patency of the calf axial, popliteal, superficial femoral and superficial venous system. As the antecedent clinical history of phlegmasia alba dolens was 10 and 30 days respectively, the failure of streptokinase to lyse the presumed original thrombus is not unexpected.

Both cases cited follow the common pattern described in the literature of the sudden development of caerulea dolens or venous gangrene within days or weeks of the development of an iliofemoral thrombosis; presumably reflecting further propagation of thrombus into tributary veins and the superficial venous system. It is precisely in this setting that thrombolytic therapy provides a theoretically attractive mode of treatment in its potential ability to lyse this fresh 'final insult' thrombus. Conversely, venous thrombectomy in the face of old axial vein clot can be anticipated to carry a high rate of reocclusion and cannot clear tributary and superficial vein thrombus.

The dramatic and undoubted improvement within 24 h of the institution of thrombolytic therapy in the two cases reported (in marked contrast to our previously limited experience with the treatment of this condition) has led to the cautious note of optimism reflected in our report.

We would presently reserve venous thrombectomy for patients with a short history of caerulea dolens or venous gangrene without a preceding history of alba dolens or where contraindications to thrombolytic therapy exist.

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Palliation of carcinoma of the oesophagus

Sir

I write to comment on the article by N. R. Saunders on intubation techniques for palliation of carcinoma of the oesophagus ('The Celestin tube in the palliation of carcinoma of the oesophagus and cardia', *Br. J. Surg.* 66, 419–421).

It is pleasing to see yet another author confirm the now widely held view that this disease is virtually incurable. He rightly implies that the only sensible course to follow is that in pursuit of maximum palliation. However, again in concert with all of the literature I have seen, he does not define what he means by the word 'palliation'. Qualitative descriptions such as 'adequate' or 'satisfactory' do not allow us to compare modes of treatment in oesophageal obstruction. This is especially troubling because almost all therapeutic manoeuvres in this distressing syndrome are fraught with morbidity and considerable mortality.

I believe it is essential to quantitate accurately palliative results by prospective study of the various treatments of oesophageal obstruction. To that end, I would draw your attention to my own work on this problem (Carcinoma of the esophagus—a new proposal for the evaluation of treatment', Stoller J. L., Samer K. J., Toppin D. I. et al. (1977) *Can. J. Surg.* 20, 454–459) in which I proposed a grade score system for the measurement of palliation. At present I am carrying out a study of palliative results in patients treated by all modes of therapy at the Cancer Control Agency of British Columbia, using the grade score system I outlined. It is my hope that, within a year or two, I will have enough data to be able to report accurately on just what happens to patients after various types of treatments in various stages of the disease.

Although lacking accurate data I must say that like many others I am thoroughly disenchanted with endo-oesophageal intubation, mainly because patients can rarely swallow anything more than blenderized food and suffer intolerable reflux. It is hard to justify a procedure with a 30 per cent inhospital mortality, which gives such poor palliation and after which the survival period is so short. My own preference at this time is for more modern types of bypass procedure, which by my own scoring system appear to be giving excellent palliation and have a much lower morbidity and mortality than that quoted by Dr Saunders. At present, however, case numbers and follow-up are not adequate for publication purposes.

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Left renal vein ligation

Sir

In their article 'Left renal vein ligation in surgery for abdominal aortic aneurysm' (*Br. J. Surg.* 66, 432), Fox and Taylor report their experience of left renal vein ligation. I would like to write and support their view that it proves to be innocuous and to draw their attention to the fact that this is so even when the renal artery has to be reimplanted for surgery on aneurysms involving the renal arteries. I have had personal experience with two such cases which were reported in the *West Indian Medical Journal* (1977), 26, 34. Both cases had ligation of the renal vein with reimplantation of the artery with 60 min of warm ischaemia, with full recovery of renal function.

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Postoperative wound infection

Sir,

I have read with interest the paper by Messrs Salem, Johnson and Devitt entitled 'Short term metronidazole therapy contrasted with povidone-iodine spray in the prevention of wound infection after appendicectomy' (*Br. J. Surg.* **66**, 430–431). It is regrettable that the authors felt they could not include a no-treatment control group in their series as the results from such a group may have helped the reader to place in perspective the observed high incidence of postoperative wound infection in the group treated with povidone-iodine.

As shown below (*Table I*), in my own controlled series involving 450 patients and three treatment groups (Gilmore and Martin, 1974) the incidence of postoperative wound infection in the control group was very similar to the incidence of infection now reported for the povidone-iodine group. Similarly, my results with povidone-iodine alone in all grades of appendicectomy closely mirror those now reported for the patients who received metronidazole prophylaxis.

Table I: INFECTION RATE RELATED TO SEVERITY OF APPENDICITIS

	Control		Povidone-iodine	
Severity	Total	Infected	Total	Infected
Normal	35	4 (11%)	37	1 (2·7%)
Inflamed	75	6 (8%)	81	2 (2·5%)
Gangrenous	26	5 (19%)	17	3 (17·6%)
Perforated	15	9 (60%)	14	6 (42·8%)

I do not accept that a significant proportion of our postoperative wounds may have been classified as sterile when they were contaminated with Bacteroides organisms since the main criteria for infection was the presence of pus. I agree that anaerobic culture techniques have improved in recent years, but we did obtain bacteriology reports from over one thousand swabs in the course of the study and we identified Bacteroides organisms from 9 appendices, 8 operative wounds and 5 postoperative wounds. In contrast, *Escherichia coli* was by far the commonest organism isolated at operation both from the appendix *in situ* (90) and from the wound prior to spraying and closure (61). It was also the organism found most frequently in the infected wounds (24). Effective prophylaxis against *E. coli* and similar organisms cannot be achieved with metronidazole whereas povidone-iodine is bactericidal against anaerobic and aerobic organisms.

It is not apparent why there should be such a variation in the demonstrated levels of efficacy of povidone-iodine prophylaxis, but what is clear is that in both series the levels of postoperative wound sepsis involving gangrenous or perforated appendices are unacceptably high. In these patients I have now adopted as a general policy the use of antibiotic cover (three doses of gentamicin and metronidazole) combined with topical prophylaxis with povidone-iodine.

In the case of normal or inflamed appendices and in other low to medium risk surgical procedures I remain convinced that topical prophylaxis with povidone-iodine dry powder spray allied to good surgical technique will minimize the incidence of postoperative wound sepsis without the risk of resistant organisms developing. This policy allows agents such as metronidazole and the aminoglycosides to be kept in reserve for use in high risk situations where they may prove invaluable.

O. J. A. GILMORE

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GILMORE O. J. A. and MARTIN T. D. M. (1974) The aetiology and prevention of wound infection in appendicectomy. *Br. J. Surg.* **61**, 281–287.

Br. J. Surg. Vol. 66 (1979) 831–832

Book reviews

Scientific Basis of Gastroenterology

Edited H. L. Duthie and K. G. Wormsley. 240 × 160 mm. Pp. 498+x. Illustrated. 1978. Edinburgh: Churchill Livingstone. £17·00.

This book aims to present to clinicians the basic science involved in understanding the derangements of gastro-enterological diseases. A team of expert and respected contributors has been assembled, mostly from the British Isles but including some from Europe, Australia and America. The presentation is good, the quality of paper being reasonable and the print clear.

The first section of the book, entitled 'Basic Principles', has chapters on gastrointestinal cell population kinetics, vasculature, immunology and hormones. These are well-written expositions of complicated topics and will be much appreciated by the non-specialist. There follow sections on secretion, absorption and motility, with 3–6 chapters in each section.

While there is naturally some variation in the structure of different chapters, they usually include not only the scientific basis but also some discussion on how this knowledge can be applied in clinical practice.

This book, at a price that must perforce be considered reasonable by modern standards, should find its way on to the bookshelves of many clinical gastroenterologists.

MICHAEL HOBSLEY

Chirurgie '78

Edited J. Patel. 240 × 160 mm. Pp. 195. Illustrated. 1978. Paris: Masson. No price given.

Chirurgie '78 is a résumé of the round-table conferences, forums and papers from the 80th French Congress of Surgery held in Paris in September 1978. It covers all aspects of surgery, including orthopaedic and vascular surgery.

There are good reviews of pancreaticoduodenectomy for chronic pancreatitis and preoperative assessment of jaundice. The emphasis is mainly gastrointestinal, but there is a useful round-table discussion on whether patients are being overtransfused and whether one can reduce the demands on blood transfusion units. Equally there is a timely review on intravenous feeding before and after surgery. Altogether the book provides a very good insight into current French surgical thought.

J.-C. GAZET

Why Not Say It Clearly? A Guide to Scientific Writing

Lester S. King. 210 × 135 mm. Pp. 186. 1978. Boston: Little, Brown. $5.95.

Complaints about the indifferent standard of medical and scientific writing date back to the founding of the Royal Society. Concern about the ability of the contemporary doctor to write clearly is continuously voiced. Recently, several short texts have been written to aid the prospective writer. This book has been written by the former senior editor of the *Journal of the American Medical Association*; the content is drawn from his experience as an editor of many years' standing and from his participation in courses on writing scientific English clearly. The depth of experience is apparent throughout the book, yet the author does not lose contact with his reader. Many of the points raised are those which the beginner finds so difficult, and his suggestions for dealing with the blank-page phenomenon shows understanding of the problems which the writer faces. His axiom that good writing means hard work, frustration and anguish will remind many of their feelings when faced with revising and rewriting manuscripts.

This book, together with others that introduce the technique of writing, should be available in medical libraries. At the price ($5.95) I would suggest that this book is worth buying for repeated study.

R. C. G. RUSSELL

Current Surgical Practice, Volume 2

Edited John Hadfield and Michael Hobsley. 240 × 155 mm. Pp. 378+xii. Illustrated. 1978. London: Arnold. £11·00.

This book contains twenty lectures all of which are concerned with surgical topics relevant to current practice. Each has been delivered at the Royal College of Surgeons by a surgeon actively engaged in clinical work who has written up his talk under the guidance of the editors. Each account is authoritative and clear and is supported by an adequate list of references and/or a bibliography. There has, of course, been some modification from the spoken word and this redrafting has allowed the text to be as up-to-date as possible. In some cases there has been considerable expansion but, none the less, many of the essays may be read in not much more time than an examiner would take to study an ideal answer to a question in the FRCS examination, which is one way in which they may be approached. However, it is evident that the authors, and the editors, have gone to a great deal of trouble to ensure that the quality of the coverage is such that this is also a volume which the qualified surgeon will wish to own and refer to frequently.

This is the second book presented under the seal of the Royal College of Surgeons, which is only right, for the series is excellent evidence of the College's continuing interest in raising the standards of surgical education.

JOHN MCFARLAND

Noninvasive Measurement of Regional Cerebral Blood Flow in Man

V. D. Deshmukh and J. S. Meyer. 235 × 160 mm. Pp. 238. Illustrated. 1978. London: SP Medical & Scientific Books. £14·00.

This is a small, well-produced and very expensive volume concerned completely with the non-invasive measurement of regional cerebral blood flow in man using intravenous, radioactive xenon. It represents the personal experience of two research workers in a laboratory in Baylor University, Houston, and contains an extremely detailed review of the subject, the personal work of the authors, and details of the establishment, contents and day-to-day running of their laboratory.

It does, however, unfortunately contain relatively few hard clinical facts. There are only 47 pages devoted to clinical applications of the method and even these are not supported by figures which would enable an accurate and objective assessment to be made. This book is undoubtedly essential to anyone who is interested in studying cerebral blood flow, but publication might be a little premature and may have been better postponed until the authors had a larger clinical experience which would have added greatly to its value to all surgeons interested in vascular and neuro-surgery.

C. W. JAMIESON

The Shoulder: Surgical and Non-surgical Management

Edited M. Post. 260×200 mm. Pp. 581+xii. Illustrated. 1978. London: Kimpton. £24·50.

ALTHOUGH fifteen authors have contributed to this publication, the editor has written most of it himself. The book is in the tradition of previous studies on the shoulder by Godman, by Moseley and by Bateman. Is there a place for yet another comprehensive work on the shoulder? It is, of course, only too easy for a reviewer to pass carping comment, and anyone who has not burnt the midnight oil in the laborious task of authorship should beware of superficial judgement, but what is one to say? A new book should certainly reflect recent advances, and in this respect it is a disappointment. Only a few chapters contain new material; the chapter on shoulder arthroplasty and total shoulder replacement stands almost alone in this regard. The chapter on radiological diagnosis does not do justice to recent radiological and other non-invasive diagnostic techniques. Dr Post's own 'Orthopaedic management of neuro-muscular disorders' is comprehensive and informative, although Howard's technique, reported in 1961, of thoraco-scapular fusion—undoubtedly the best mode of stabilizing the scapula in appropriate cases—is surprisingly not mentioned. It is difficult to justify the inclusion of a chapter on 'Antimicrobial therapy in orthopaedic patients' as if it differed in the shoulder from elsewhere, and somewhat surprisingly, no less than 8 pages are devoted to the management of unstable thoracic injuries. Enthusiasts are liable to stretch the boundaries of their subject, but is this not going too far?

However much a reviewer may carp, this publication is clearly a labour of love, and who would argue with Tennyson that 'tis better to have loved and lost than never to have loved at all?

LIPMAN KESSEL

Les Tumeurs Oddiennes

Professor Marchal and Professor Hureau. 240×160 mm. Pp. 180. Illustrated. 1978. Paris: Masson. No price given.

Les Tumeurs Oddiennes (ampullary tumours of Vater) by Professors Marchal and Hureau is an extensive but succinct 180-page review with 430 world-wide references quoted. It attempts to answer three questions: whether these tumours are always malignant, whether diagnosis has been improved by modern techniques, in particular endoscopy, and finally, whether these lesions should be treated by major ablative surgery or by local excision. 'Tumeurs Oddiennes' are defined as tumours of the biliary, pancreatic and duodenal junction, excluding periampullary lesions. A comparison is made between 736 French cases and 1089 from the world literature. Considering one section, where surgery was undertaken, the French series had a resectability rate of 78·7 per cent compared with 87·2 per cent in the world series. Of interest, 19·2 per cent had a papillectomy compared with only 6·6 per cent in the latter series and there was a correspondingly low mortality of 9·1 per cent compared with 19·6 per cent in the world series. Generally, pancreaticoduodenectomy had a 19·4–17·7 per cent mortality.

The chance of surviving 5 years after papillectomy was the same in both series at 30 per cent excluding operative deaths. This is considerably better than that following pancreaticoduodenectomy, at 19·4 per cent in the French series and from 6·3 to 54 per cent in the world series.

The questions of preoperative assessment, selection of cases and evaluation of postoperative problems are thoroughly discussed.

This is an extremely good monograph from the French Association of Surgery and should be read by all those interested in malignant disease of this area. It is well worth translating into English.

J.-C. GAZET

Mnemonics and Tactics in Surgery and Medicine

J. J. Shipman. 170×105 mm. Pp. 308. Illustrated. 1979. London: Lloyd-Luke. £4·50.

SOME lists of facts in medicine and surgery do not fit together in a logical and easily remembered pattern. One way of recalling them is to form mnemonics. Home-made mnemonics are best; by the time the list has been tailored to fit the chosen key word, the list is so imprinted on the memory that the key word can be forgotten. Some gems become classics and should be preserved. The very best are anatomical mnemonics and unprintable.

John Shipman's friends have for years been regaled by the latest finding, and he has now published his collection in paperback, relating to general medicine and general surgery. Also included are succinct notes on how to deal with clinical problems, and a few cartoons. The best mnemonics are short, simple, and significant. For instance, if an enlarged lymph node is detected we are reminded by the words PALS to examine the Primary site, All other glands, the Liver and Spleen. Some lists are too long, or the references are too obscure to remember, but are otherwise enjoyable. For instance, I had not previously encountered the name of my distinguished Royal Free Hospital colleague, Sheila Sherlock, as an apt mnemonic for the results of hepatic damage.

It was right that these should be recorded. I hope that John Shipman will continue to collect them for future editions, since he has become the self-appointed HAM (Honorary Archivist of Mnemonics).

R. M. KIRK

Nouveau Traité de Technique Chirurgicale: Volume 15

Professor Couvelaire and Professor Cukier. Second edition. 260×190 mm. Pp. 856+xiv. Illustrated. 1978. Paris: Masson. No price given.

THE *Nouveau Traité de Technique Chirurgicale* is a series in 15 volumes of French surgical technique, and in many ways is similar to British texts such as Robb and Smith, though it relies more on the written word than on illustrations. The volume reviewed here, number 15 in the series, is on urology. The contents are listed both in French and English. Each chapter deals with each organ or structure according to standard orthodox practice. The text is well illustrated with explicit, sharp, well-drawn, step-by-step figures. The text is clear, concise and carefully worded. However, it is a manual of operative surgery and, whereas all current procedures are described, it does not deal in depth with the indications for surgery or the complications. For example, renal transplantation is dealt with as a surgical exercise, not as a subject for discussion.

This is an excellent textbook, to be read in the original, but it would not fill a gap if translated as there are similar excellent texts in the English language.

J.-C. GAZET

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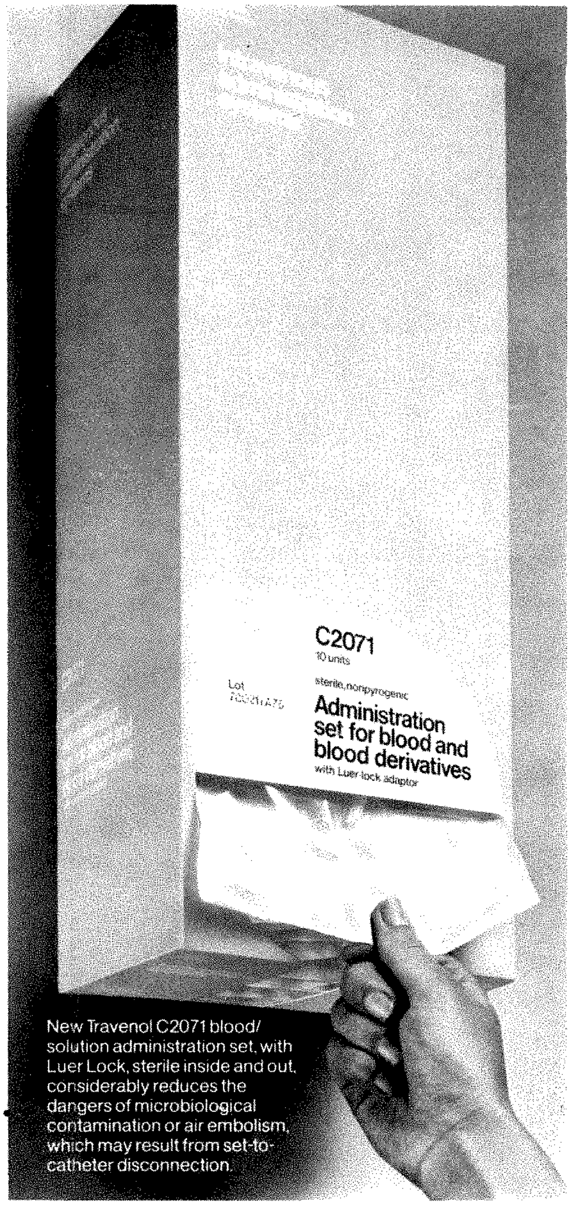

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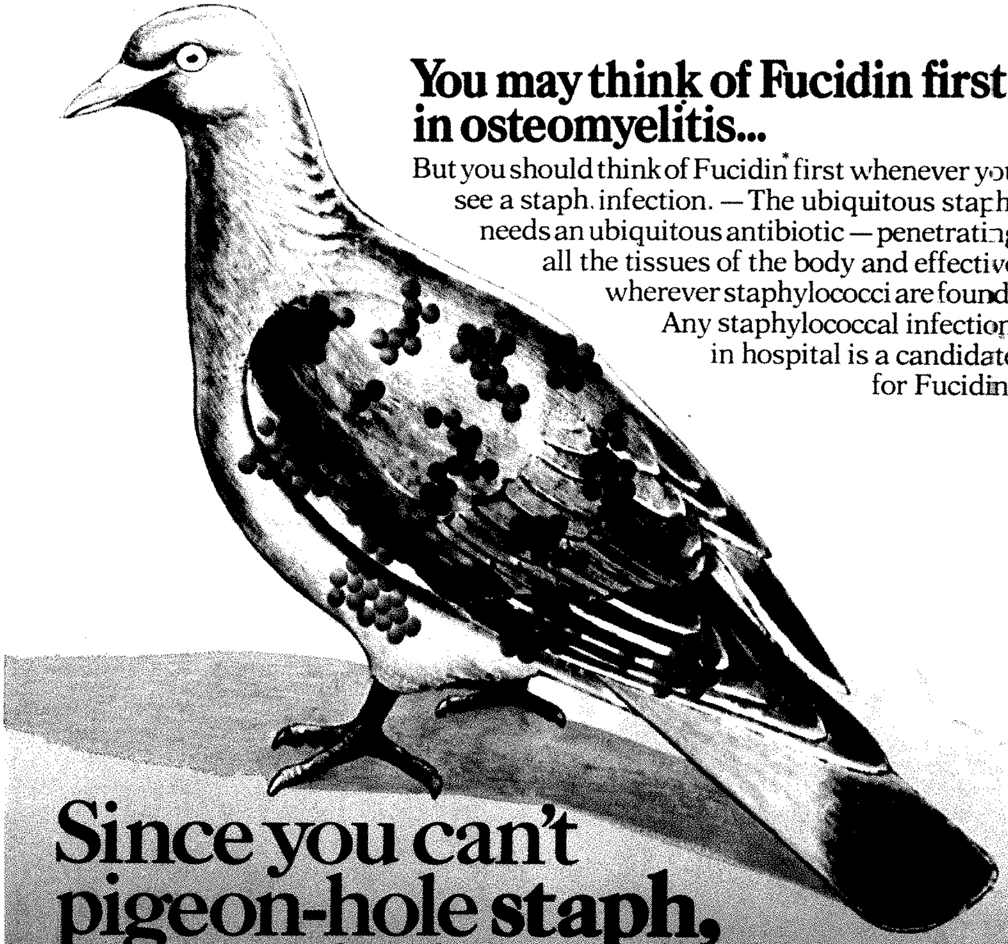

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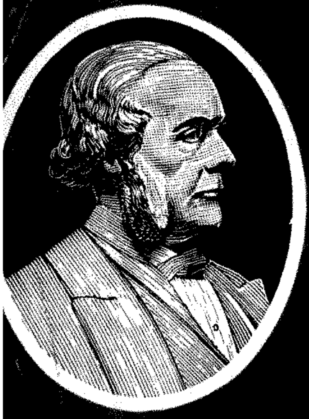

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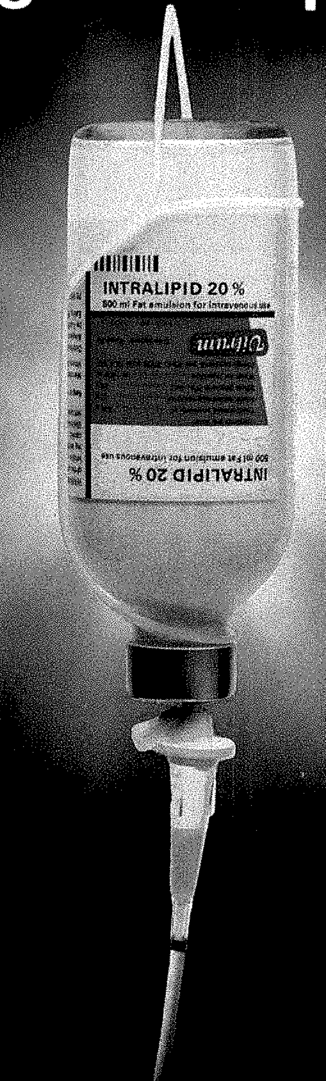
How to strengthen the post-op life line



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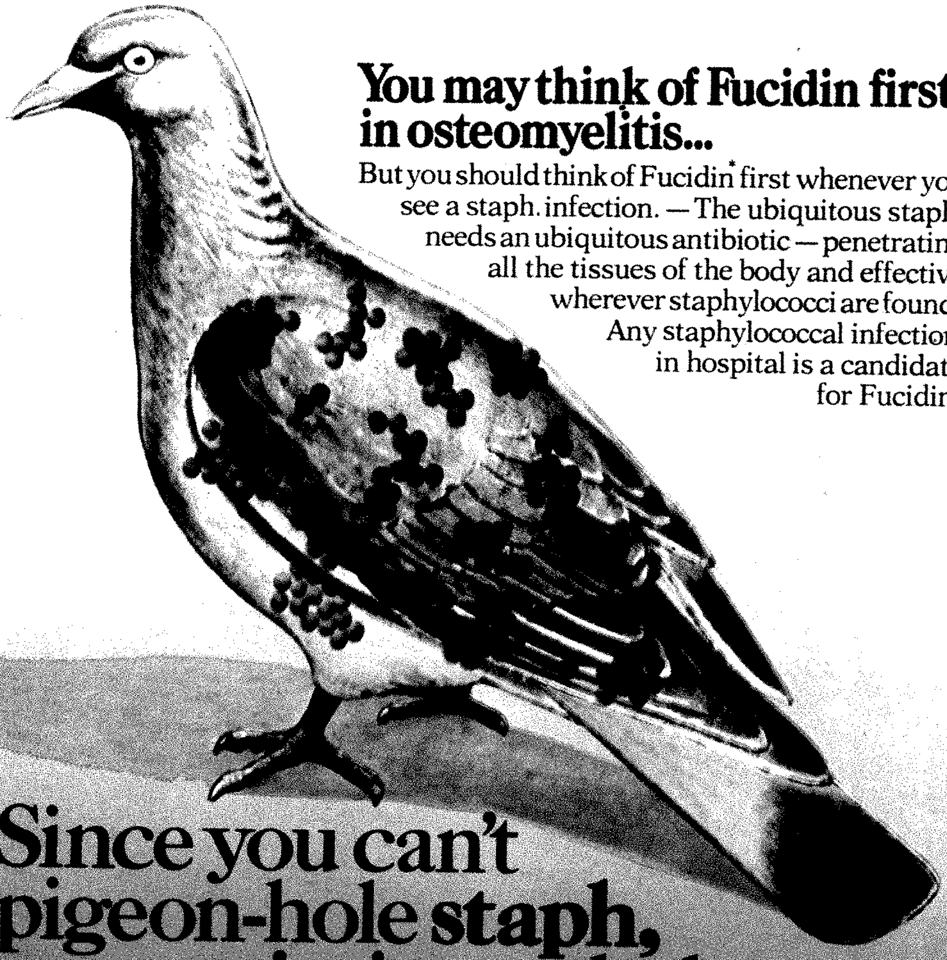

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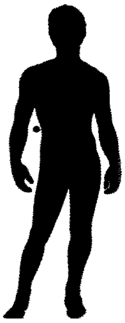

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References
1, Bistrian, B.R., Blackburn, G.L., Vitale, J., Cochran, D., and Naylor, J. (1976). Prevalence of malnutrition in general medical patients. Journal of American Medical Association, 235, 1567-1570.
2. Hill, G.L., Pickford, I., Young, G.A., Schorah, C.J., Blackett, R.L., Burkinshaw, L., Warren, J. V., and Morgan, D.B. (1977) Malnutrition in surgical patients – An unrecognised problem. Lancet, *i*, 689-692.
3. Daly, J.M., Vars, H.M., and Dudrick, S.J. (1972) Effects of protein depletion on strength of colonic anastomoses. Surgery Gynec. Obstet., *134*, 15-21.
4. Alexander, J.W. (1974). Emerging concepts in the control of surgical infections. Surgery *75*, 934-946.

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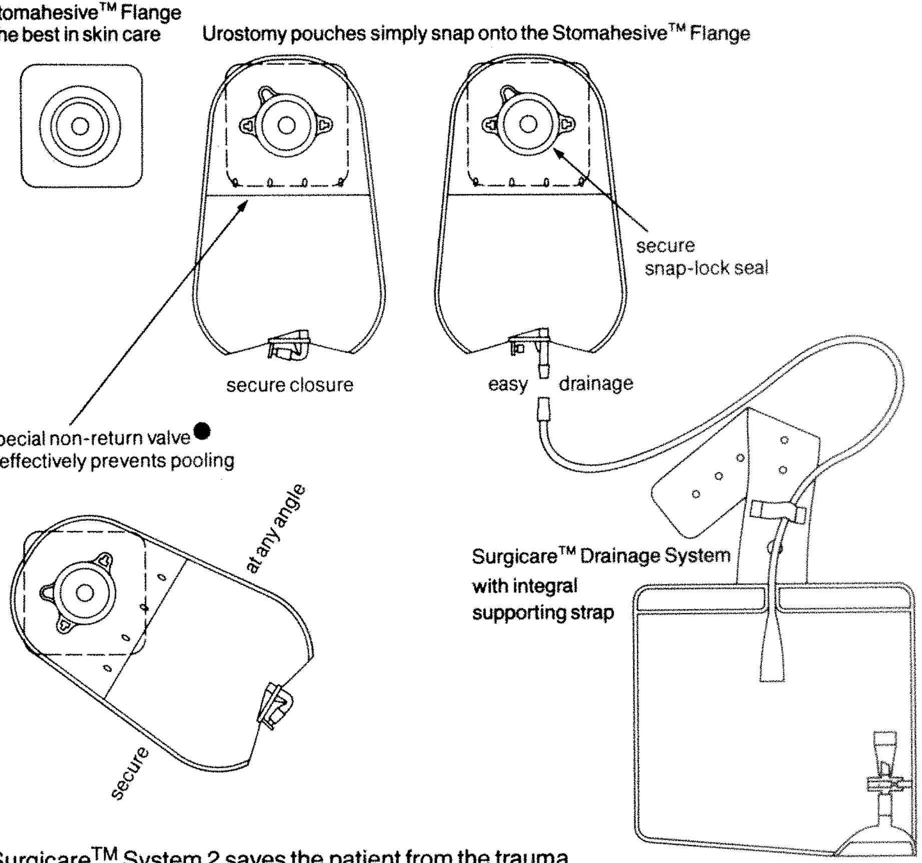
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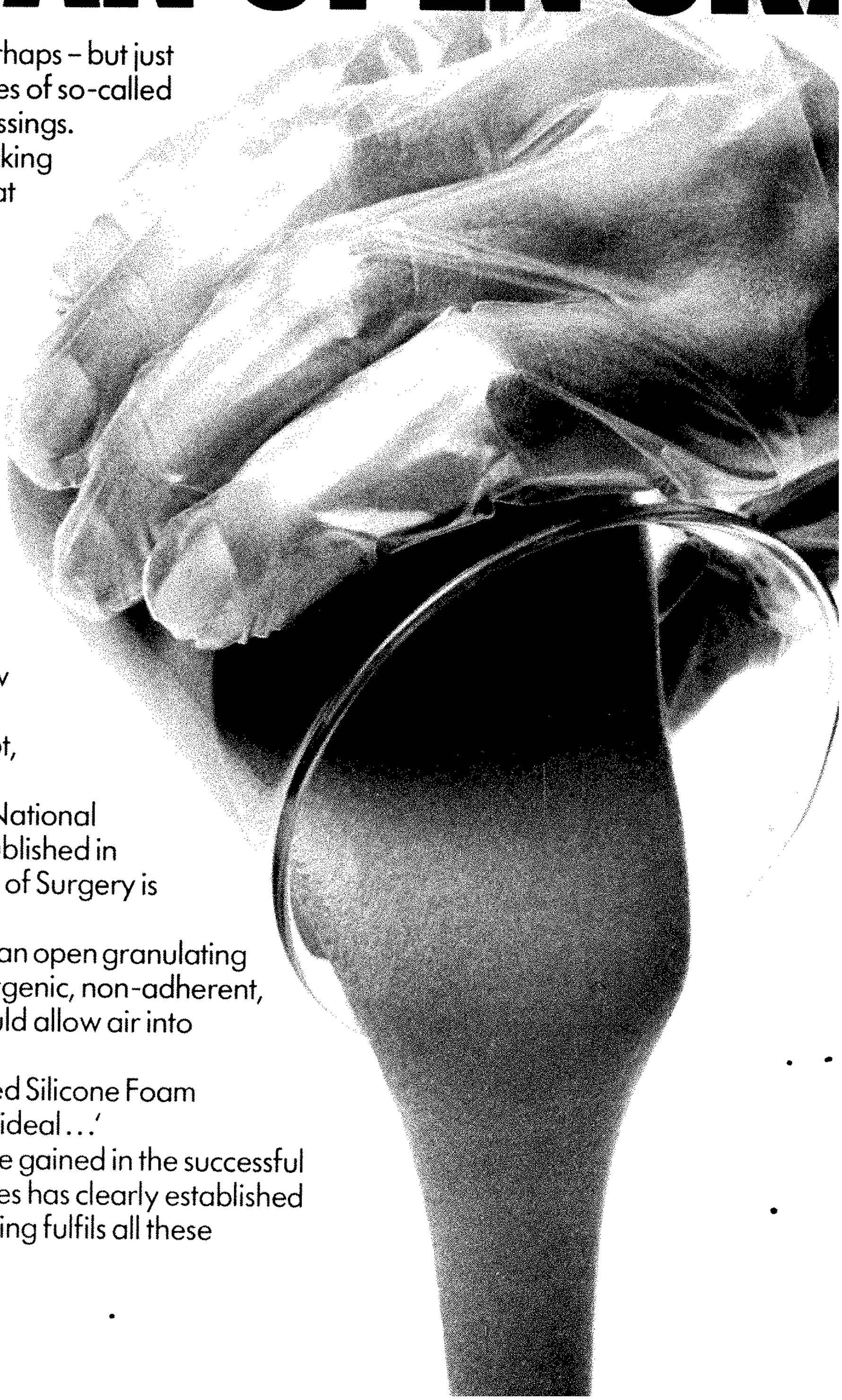

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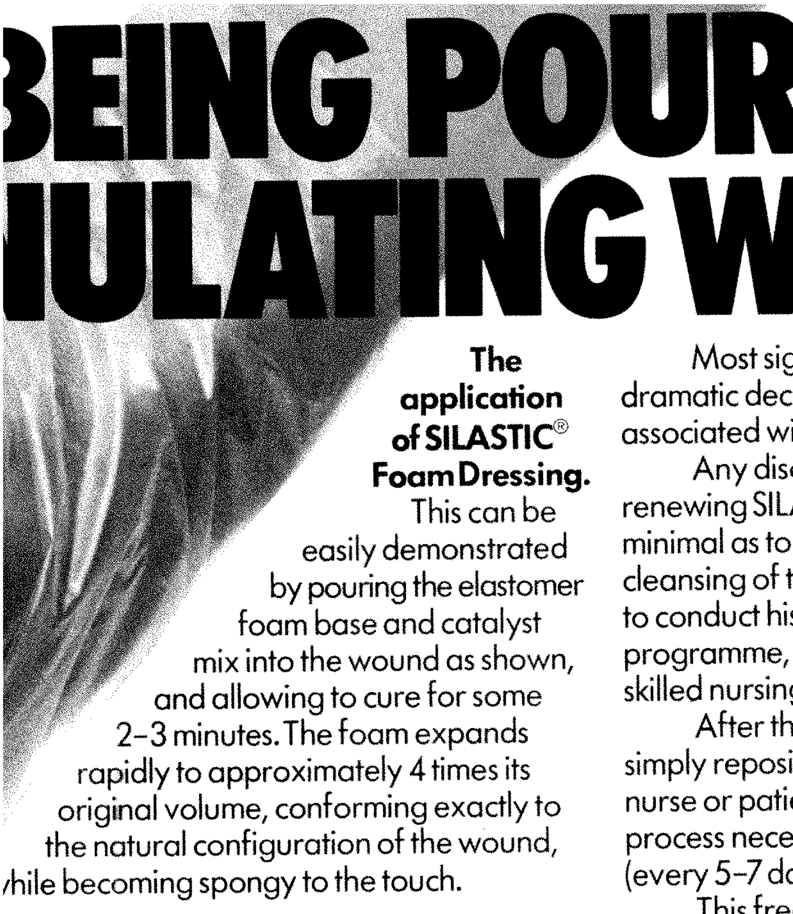

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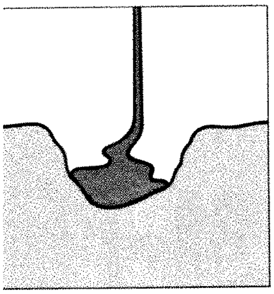

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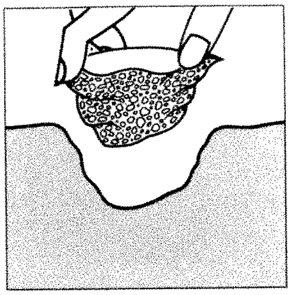

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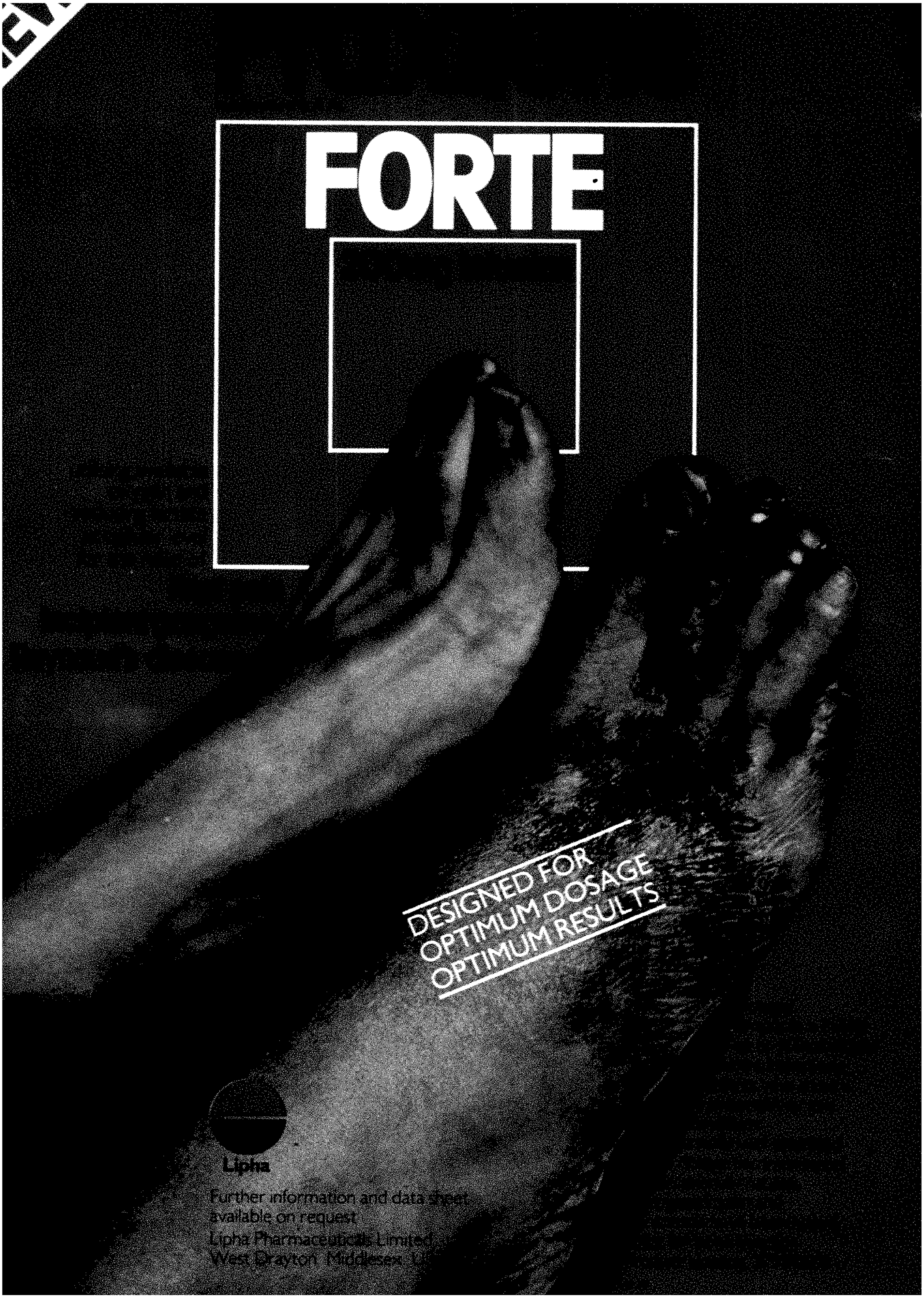

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The Fourth Joint Meeting of the Societies took place at the Nuffield Department of Surgery, University of Oxford, on 5, 6 and 7 July 1979, with Professor H. L. Duthie (President of the Surgical Research Society) in the Chair.

Adjuvant cytotoxic liver perfusion for colorectal cancer

I. TAYLOR, J. ROWLING AND C. WEST*

SUMMARY

Colorectal liver metastases develop by malignant cells entering the portal venous circulation. A randomized prospective clinical trial was commenced in 1975 to assess the value of adjuvant umbilical vein cytotoxic perfusion (with 5-fluorouracil) following colorectal resection.

One hundred and fifty-four patients without macroscopic liver secondaries have so far entered the trial. The mean age, sex, site and stage of the disease were similar in the control and perfusion groups and there was no statistically significant difference in postoperative complications or hospital stay (17·1 ± 7·9 days control, 15·8 ± 7·4 days perfusion group).

So far, 23 deaths have occurred in the control group (20 due to recurrent disease) and 7 in the perfusion group (5 due to recurrent disease). Liver metastases were present in 13 control patients and 2 perfusion patients.

These results show an encouraging trend and suggest that adjuvant cytotoxic liver perfusion may reduce the development of colorectal liver metastases and hence improve the subsequent prognosis.

COLORECTAL cancer now accounts for approximately one-seventh of all deaths from malignant disease and is the second commonest cancer in this country. Throughout the past 25 years, despite great improvements in surgical techniques, the annual death rate has remained disappointingly high. Reported crude 5-year survival rates of all patients admitted with colorectal cancer to general hospitals have been consistently low at about 20 per cent (Slaney, 1971; Gill and Morris, 1978).

In patients seen in district general hospitals approximately 30 per cent of tumours are disseminated and incurable on admission and between 30 and 60 per cent of cases are admitted as acute emergencies (Till, 1977). Excluding these groups, the overall 5-year survival rate is still only 50 per cent (Slaney, 1971).

A prominent cause of death in patients surviving the initial surgery is the development of liver metastases. Cedermark et al. (1977) recently reported 456 patients who died of large bowel cancer and at autopsy the liver was involved with metastases in 48 per cent of cases.

Colorectal micrometastases reach the liver via the portal vein. In an attempt to reduce the subsequent development of macroscopic liver metastases a randomized trial of adjuvant cytotoxic liver perfusion given via the 'obliterated' umbilical vein during the first 7 postoperative days has been performed and patients have been followed for up to 46 months. The results of an initial pilot study have been published previously (Taylor et al., 1977).

Patients and methods

One hundred and fifty-four consecutive patients with primary adenocarcinoma of either the colon or rectum but without macroscopic liver secondaries have entered the study over the past 46 months. In the majority of cases a preoperative $^{99}Tc^m$ sulphur colloid liver scan was performed and in all patients preoperative haematological and liver function tests were carried out. More recently, ultrasound scanning of the liver has been included.

By means of the closed envelope technique 66 patients were randomly allocated preoperatively to receive adjuvant liver perfusion in addition to surgical resection. In contrast, 73 patients underwent surgical resection alone. Eleven further patients were randomized but were subsequently excluded from the study owing to the discovery of unexpected liver metastases at operation in 3, hepatic cirrhosis in 2 and because of technical difficulties in cannulating the umbilical vein in 6 patients.

Standard surgical techniques of resection were adhered to, the actual procedure to be performed being left to the discretion of the operator. In patients randomized to receive adjuvant perfusion the umbilical vein was dissected from the falciform ligament and cannulated as previously described (Kessler and Zimmon, 1967; Lavoire et al., 1967; Mann et al., 1974; Taylor et al., 1977). One gramme of 5-fluorouracil was given in 5 per cent dextrose daily by continuous perfusion for the first 7 postoperative days. Heparin (5000 u/d) was

---

* Departments of Surgery and Biostatistics, University of Liverpool.

Correspondence to: I. Taylor, Department of Surgery, University of Liverpool.

Table I: SITE, STAGE AND DEGREE OF DIFFERENTIATION

	Control			Perfusion		
Stage	*A*	*B*	*C*	*A*	*B*	*C*
Ascending/transverse colon	2	4	3	2	8	5
Descending/sigmoid colon	1	11	5	3	10	5
Rectosigmoid/rectum	4	22	17	2	15	14
Total	7	37	25	7	33	24
Degree of differentiation						
Well	40 (58%)			34 (53%)		
Moderately	19 (27%)			25 (39%)		
Poorly/anaplastic	8 (13%)			5 (8%)		

Table II: POSTOPERATIVE MORBIDITY

	Control ($n = 69$)	Perfusion ($n = 64$)
Wound infection	23	18
Anastomotic dehiscence	7	3
Alopecia		1
Oral ulceration		2
Transient leucopenia		5
Transient thrombocytopenia		3
Mean hospital stay (d)	17·1 ± 7·9	15·8 ± 7·4

Table III: POSTOPERATIVE MORTALITY

Control ($n = 5$)	Perfusion ($n = 5$)
2 myocardial infarction	1 pulmonary embolus
1 Gram-negative septicaemia	2 myocardial infarction
2 bronchopneumonia (with faecal fistula)	1 bronchopneumonia and Gram-negative septicaemia (leucopenia and thrombocytopenia)

Table IV: DEATHS DURING FOLLOW-UP

	Control			Perfusion		
Stage	*A*	*B*	*C*	*A*	*B*	*C*
Ascending/transverse colon	—	—	1	—	—	—
Descending/sigmoid colon	—	1	4	—	—	—
Rectosigmoid/rectum	1	4	12	—	2	5
Total	1	5	17	—	2	5
Liver metastases alone		5			1	
Liver metastases and metastases elsewhere		8			1	
Local recurrence alone		7			4	

added to the perfusate primarily to discourage portal vein thrombosis.

Postoperative blood counts and liver function tests were performed on alternate days for the first 10 postoperative days. A portal venogram was performed during the first 48 h to ensure that the catheter was well positioned and was perfusing equally both main portal branches. If not, the catheter was manipulated under the image intensifier until adequate perfusion was achieved.

The operative specimens were examined and the growths classified according to Dukes' categorization (A, B, C) of the extent of spread. The degree of differentiation was also noted.

The patients were seen at monthly intervals in the outpatient department for the first 3 months and then at 3-monthly intervals for 1 year. They were then assessed at 6-monthly intervals.

Liver function tests, ^{99}Tc^{m} sulphur colloid liver scans and, more recently, ultrasound scanning of the liver were repeated at intervals.

Results

Age and sex

The mean age of the patients in the control group was 64·4 ± 10·1 years and that of patients in the perfusion group was 63·4 ± 11·1 years. There were 44 males in the control group and 34 in the perfusion group.

Site and stage

The site and stage of each tumour are shown in *Table I*. Because of the relatively small numbers of patients, the groups have been divided into colonic and rectal (including rectosigmoid) tumours. There was no statistically significant difference between the Dukes' categorization of the tumour in each group ($\chi^2 = 0·0617$, d.f. = 2, $P = 0·96$).

There was no statistically significant difference in the degree of differentiation of the tumours in the two groups (*Table I*).

The surgeon's subjective impression of the degree of local infiltration was recorded. The tumour was mobile in 27 controls and 24 perfusion patients, moderately attached in 19 controls and 12 perfusion patients and fixed with probably macroscopic tumour remaining in 21 control and 24 perfusion patients.

Postoperative morbidity

Twenty-three patients (30 per cent) in the control group and 18 (28 per cent) in the perfusion group developed a wound infection. The chief organisms were *Escherichia coli* and bacteroides. Anastomotic leaks occurred in 7 controls and 3 perfusion patients (*Table II*).

One patient developed partial alopecia and 2 others had transient oral ulceration during perfusion. The mean postoperative hospital stay was 17·1 ± 7·9 days in the control group and 15·8 ± 7·4 days in the perfusion group. These differences were not statistically significant.

Postoperative mortality

In the immediate postoperative period there were 10 deaths: 5 in the control and 5 in the perfusion group. Necropsy was carried out in all cases. The cause of death in each patient is shown in *Table III*. It was considered that the cytotoxic perfusion was a contributory factor in 1 patient. This 65-year-old woman had a large carcinoma of the rectum surrounded by an abscess cavity. Abdominoperineal excision was performed and she was randomized to receive cytotoxic perfusion. On the ninth postoperative day she developed extensive bronchopneumonia and Gram-negative septicaemia. At this time she had marked leucopenia and thrombocytopenia.

Laboratory investigations

Five patients developed transient leucopenia (2·3, 3·2, 1·5, 1·1 and 2·1 × 10^9/dl) and 3 transient thrombocytopenia (55, 40, 35 × 10^9/dl) during perfusion. All values returned to normal on completion of perfusion. The white cell count was statistically significantly lower between the sixth and tenth days in the perfusion group compared with the control group (*Fig.* 1). However, the values returned towards normal on completion of perfusion.

Both groups had disturbed liver function values during the first 10 postoperative days (*Fig.* 2). In all patients, the mean values for bilirubin, alkaline phosphatase, AST, ALT and LDH increased between the second and tenth postoperative days. The levels in patients undergoing perfusion were not statistically significantly different from those in the control patients except during the second postoperative day when the mean AST levels were greater in the perfusion patients (*Fig.* 2).

Follow-up
In patients so far followed up for more than 1 year (47 control, 43 perfusion) the mean period of follow-up is 25·9 ± 9·7 months in the control and 27·9 ± 10·7 months in the perfusion patients.

Twenty-three patients have died in the control group and 7 patients in the perfusion group (*Table IV*). In the control group, 5 had multiple liver metastases alone, 8 had generalized metastases as well as liver metastases and 7 had local recurrence only. One patient in the perfusion group had liver metastases alone, 1 had liver metastases as well as metastases elsewhere and 4 had local recurrence. The incidence of patients with liver metastases in the two groups (13 control, 2 perfusion) was statistically significantly different ($\chi^2 = 6{\cdot}70$, $P < 0{\cdot}01$). The incidence of local recurrence between the two groups was not statistically significantly different.

One other control and one other perfusion patient are known to have local recurrence.

Discussion

The liver contains secondary deposits in about one-third to one-half of fatal cases of colorectal malignancy (Brown and Warren, 1938; Willis, 1948; Cedermark et al., 1977). Once liver metastases have developed the prognosis is bleak. Bengmark and Hafstrom (1969) found an incidence of liver metastases at laparotomy of 24·5 per cent with a mean survival of 5·1 months. Other series have also emphasized the poor outlook in these patients (Pestana et al., 1964; Jaffe et al., 1968; Taylor, 1978). It has been estimated that as many as 50 per cent of colorectal cancers will sooner or later give rise to liver metastases (Bengmark and Hafstrom, 1969) and the survival rate seems to be the same in these patients whether a palliative resection of the colon is performed or some form of bypass procedure is carried out. This argues in favour of hepatic metastases constituting a chief factor in the survival of these patients.

A great deal of work has been carried out to determine the factors that influence the development of liver metastases. A simplistic explanation would be that tumour cells embolize into the portal venous system via the invaded mesenteric veins and enter the liver. There is evidence to support this view. Brown and Warren (1938) found venous invasion by tumour in 41 per cent of necropsy cases. In operative specimens of rectal cancer evidence of venous spread is found in approximately 17 per cent (Dukes, 1957). However, the absence of intravascular permeation of tumour cells does not exclude the possibility of venous spread since malignant emboli may have been discharged into the blood stream, leaving no trace behind them.

Fisher and Turnbull (1955) recovered tumour cells from the blood of major mesenteric venous channels in 32 per cent of cases of colorectal carcinoma at surgery. They suggested that manipulation of the

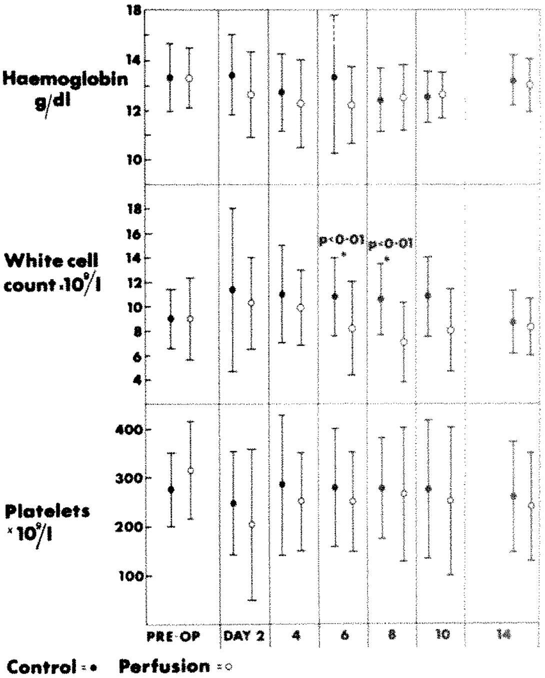

Fig. 1. Haematological investigations during the postoperative period in each group.

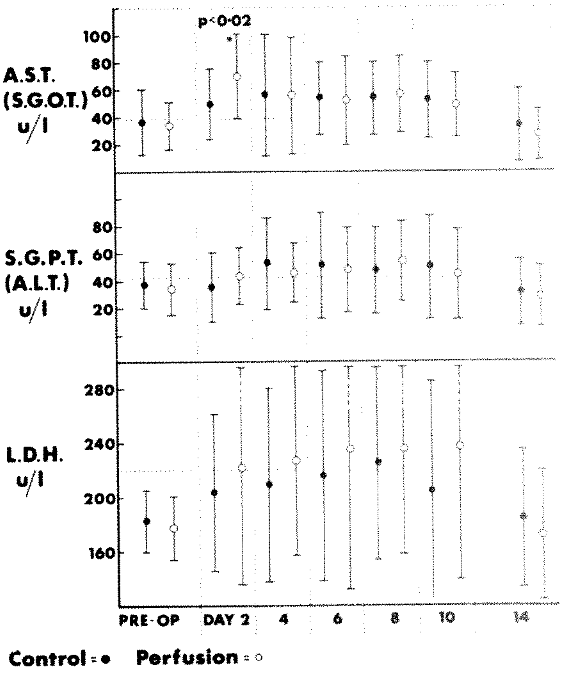

Fig. 2. Liver function tests during the postoperative period in each group.

neoplasms may result in venous dissemination of tumour cells. These findings have been confirmed in other studies (Engell, 1955; Pruitt et al., 1958; Roberts et al., 1958).

Nevertheless, in clinical terms, not all circulating cancer cells give rise to metastases. Several reports have shown that patients with malignant cells in the venous blood fare no worse than those without (Engell, 1955; Roberts et al., 1961; Sellwood et al., 1965). Also, there is little evidence that manipulation *per se* can increase the number of malignant cells discharged into the circulation. However, the added effect of operative stress has been shown on an experimental basis to produce an increase in the incidence of hepatic metastases by improving the chances of survival of cells and allowing them to establish growth within the liver (Buinauskas et al., 1958; Fisher and Fisher, 1959). Similarly, the induction of anaesthesia increases the incidence of circulating malignant cells (Griffiths et al., 1973).

The majority of tumour cells, however, will be destroyed and thus have no pathogenic potential. Some undoubtedly survive and remain dormant within the liver until some form of stimulus (perhaps an immunological one) activates their growth into a micrometastasis which penetrates the interstitial space. Since this stimulus is not as yet known, it seems sensible to try to prevent this dissemination or indeed destroy the cells entering the portal venous system.

Various cytotoxic agents have been utilized in an experimental situation to try to reduce the number of 'takes' of tumour. Cruz et al. (1956) showed that nitrogen mustard was effective in reducing the percentage of 'takes' of the carcinosarcoma tumour in rats when given within an hour of inoculation of cancer cells. Morales et al. (1957) suggested that the drug must be given at the time of inoculation and continued for some time after in order to achieve a significant reduction in the number of takes. Sporadic clinical reports have appeared in the literature advocating intraportal injection of cytotoxic agents at the time of surgery for colorectal cancer in an attempt to diminish the numbers of circulating tumour cells (Morales et al., 1957). Other surgeons (Turnbull, 1970) prefer a 'no-touch isolation' technique during resection and follow-up studies of 5-year survival using this technique yield impressive results.

In this study the primary aim was to assess the possible benefit of adjuvant perfusion of large doses of 5-fluorouracil into the portal venous system in reducing the incidence of liver metastases. It was hoped that preoperative screening techniques (liver function tests, liver scans and ultrasound of liver) and careful palpation of the liver at operation would ensure that patients with liver metastases at the time of initial laparotomy were excluded.

The actual method of liver perfusion through the umbilical vein was relatively simple to perform although cannulation proved technically impossible in 6 patients who were thus excluded from the study. The chief difficulty occurs in patients who have had previous upper abdominal surgery and in whom the falciform ligament has been divided. Since the liver metabolizes 5-fluorouracil, large doses could be given over 7 days with few systemic side-effects. Those that did occur, however, were troublesome—alopecia and oral ulceration. One patient with a carcinoma of the rectum and localized perirectal abscess formation developed postoperative Gram-negative septicaemia with leucopenia and thrombocytopenia. She eventually died and post-mortem showed severe bronchopneumonia with evidence of septic microemboli within the liver. It is considered that cytotoxic perfusion contributed to her death and accordingly patients with intra-abdominal sepsis are now no longer included for cytotoxic perfusion.

Apart from this single patient, the results of adjuvant liver perfusion in colorectal cancer appear encouraging. During the period of follow-up 23 patients have died in the control group compared with 7 in the perfusion group. Thirteen of the control patients have developed multiple liver metastases compared with 2 patients in the perfusion group. It is apparent that patients with Dukes' C lesions were particularly benefited. Forty-seven patients with Dukes' C lesions were included in the study and 22 have died during the period of follow-up—17 in the control group and 5 in the perfusion group.

Although the results are superficially promising, the period of follow-up is still relatively short and the number of patients too small to make accurate statistical conclusions. There is evidence that the incidence of liver metastases is reduced during the first few postoperative years although it is unlikely that the incidence of either local recurrence or peritoneal metastases will be materially reduced in the long term. However, it is feasible that this technique could be combined with others, e.g. adjuvant radiotherapy or immunotherapy, to reduce these sequelae.

Finally, it should be mentioned that heparin was initially included in the perfusion to discourage portal vein thrombosis but conceivably it could have a separate action in preventing the deposition of a fibrin clot around micrometastases (Hilgard et al., 1972). Other workers have shown that heparin may well have a valuable role to play in the prevention of liver metastases (White et al., 1976). This trial will not distinguish between the actions of 5-fluorouracil and those of heparin alone.

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References

BENGMARK S. and HALSTROM L. (1969) The natural history of primary and secondary malignant tumours of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. *Cancer* **23**, 198–202.

BROWN C. E. and WARREN S. (1938) Visceral metastases from rectal carcinoma. *Surg. Gynecol. Obstet.* **66**, 610–614.

BUINAUSKAS P., MCDONALD G. O. and COLE W. H. (1958) Role of operative stress on the resistance of the experimental animal to inoculated cancer cells. *Ann. Surg.* **148**, 642–650.

CEDERMARK B. J., SCHULTZ S. S., BAKSHI S. et al. (1977) The value of liver scan in the follow-up study of patients with adenocarcinoma of the colon and rectum. *Surg. Gynecol. Obstet.* **144**, 745–748.

CRUZ P., MCDONALD G. O. and COLE W. H. (1956) Prophylactic treatment of cancer. *Surgery* **40**, 291–296.

DUKES C. E. (1957) Discussion on major surgery in carcinoma of the rectum, with or without colostomy, excluding the anal canal and including the rectosigmoid. *Proc. R. Soc. Med.* **50**, 1031–1052.

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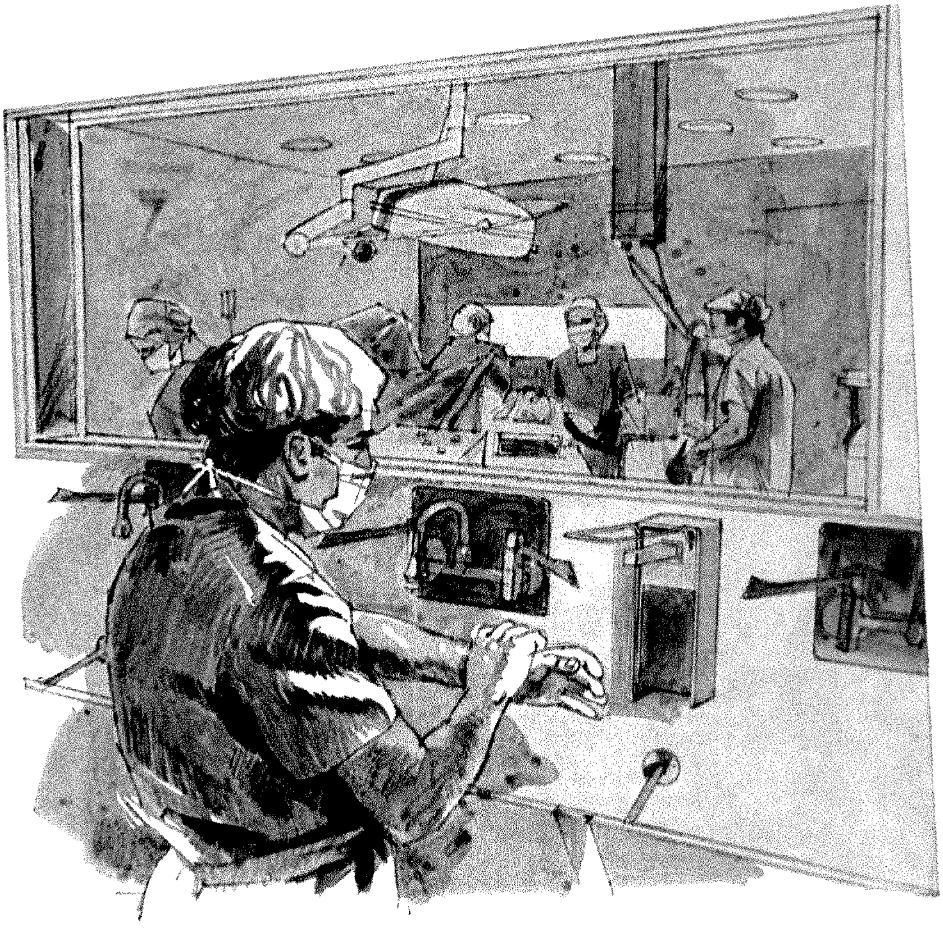

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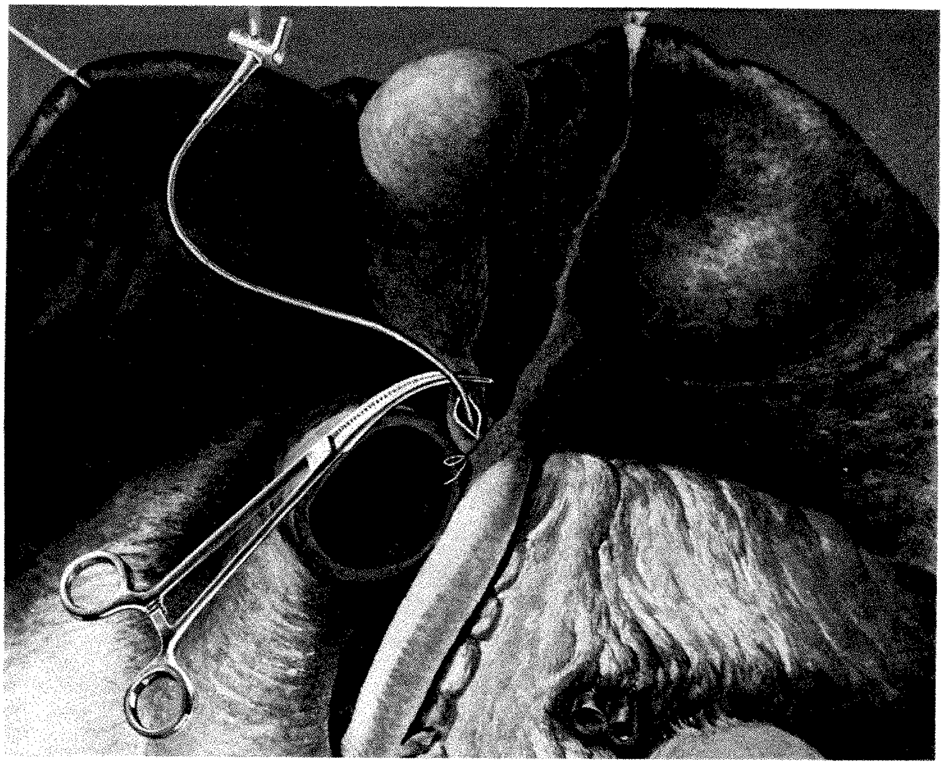

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ENGELL H. C. (1955) Cancer cells in the circulating blood. *Acta Chir. Scand.* Suppl. 201.

FISHER B. and FISHER E. R. (1959) Experimental studies of factors influencing hepatic metastases. III. Effect of surgical trauma with special reference to liver injury. *Ann. Surg.* **150**, 731–743.

FISHER E. R. and TURNBULL R. B. (1955) The cytological demonstration and significance of tumour cells in the mesenteric venous blood in patients with colorectal cancer. *Surg. Gynecol. Obstet.* **100**, 102–107.

GILL P. G. and MORRIS P. J. (1978) The survival of patients with colorectal cancer treated in a regional hospital. *Br. J. Surg.* **65**, 17–20.

GRIFFITHS J. D., MCKINNA J. and ROWBOTHAM H. D. (1973) Carcinoma of the colon and rectum. Circulating malignant cells and five-year survival. *Cancer* **31**, 226–236.

HILGARD D., BEYERLE R., HOHAGE V. et al. (1972) The effect of heparin on the initial phase of metastases formation. *Eur. J. Cancer* **8**, 347–352.

JAFFE B. M., DONEGAN W. L., WATSON F. et al. (1968) Factors influencing survival in patients with untreated hepatic metastases. *Surg. Gynecol. Obstet.* **127**, 1–11.

KESSLER R. E. and ZIMMON D. J. (1967) Umbilical vein catheterization in man. *Surg. Gynecol. Obstet.* **65**, 594–597.

LAVOIRE P., LEGARE H. and DIALLET A. (1967) Portal catheterization via the round ligament of the liver. *Am. J. Surg.* **114**, 822–830.

MANN B., KRAUS L. and PIKIELNY S. (1974) Investigations of the portal circulation via the umbilical vein. *Vasc. Surg.* **8**, 193–202.

MORALES F., BELL M., MCDONALD G. D. et al. (1957) The prophylactic treatment of cancer at the time of operation. *Ann. Surg.* **146**, 588–595.

PESTANA C., REITEMEIER R. J., MOERTEL C. G. et al. (1964) The natural history of carcinoma of the colon and rectum. *Am. J. Surg.* **108**, 826–829.

PRUITT J. E. A., HILBERG A. W. and KAISER R. F. (1958) Malignant cells in peripheral blood. *N. Engl. J. Med.* **259**, 1161–1170.

ROBERTS S., JONASSON O., LONG L. et al. (1961) Clinical significance of cancer cells in the circulating blood. Two- to five-year survivals. *Ann. Surg.* **154**, 362–371.

ROBERTS S., WATNE A., MCGRATH R. et al. (1958) Technique and results of isolation of cancer cells from the circulating blood. *Arch. Surg.* **76**, 334–340.

SELLWOOD R. A., KAPPER S. W. A., BURN J. I. et al. (1965) Circulating cancer cells: the influence of surgical operations. *Br. J. Surg.* **52**, 69.

SLANEY G. (1971) In: IRVINE W. (ed.) *Modern Trends in Surgery*, 3. Sevenoaks, Butterworths, pp. 69–89.

TAYLOR I. (1978) Cytotoxic perfusion for colorectal liver metastases. *Br. J. Surg.* **65**, 109–114.

TAYLOR I., ROWLING J. T. and BROOMAN P. (1977) Adjuvant liver perfusion in colorectal cancer: initial results of a clinical trial. *Br. Med. J.* **2**, 1320–1322.

TILL A. S. (1977) In: TRUELOVE S. C. and LEE E. (ed.) *Topics in Gastroenterology*, 5. Oxford, Blackwell Scientific, pp. 77–85.

TURNBULL R. B. (1970) Cancer of the colon: 5–40-year survival rates following resection utilizing the isolation technique. *Ann. R. Coll. Surg. Engl.* **46**, 243–350.

WHITE H., GRIFFITHS J. D. and SALSBURY A. J. (1976) Circulating malignant cells and fibrinolysis during resection of colorectal cancer. *Proc. R. Soc. Med.* **69**, 467–470.

WILLIS R. A. (1948) *The Pathology of Tumour*. Sevenoaks, Butterworths, pp. 422–425.

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A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial

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SUMMARY

A controlled, prospective study comparing streptokinase and heparin treatment has been completed in 51 patients presenting with acute proximal venous thrombosis of less than 8 days' clinical duration. Patients were studied by means of pre-treatment, post-treatment, 3- and 12-monthly phlebography and pulmonary perfusion scanning and were followed up at 3-monthly intervals.

Of the 26 patients randomized to receive streptokinase, therapy was stopped in 3 because of complications. Phlebography 5 days after starting treatment showed 80–100 per cent lysis in 17 of the 23 patients who completed the course of streptokinase. Two patients later developed partial rethrombosis. One patient developed an asymptomatic pulmonary embolus during treatment. During follow-up (mean 19 months) only 1 of the 17 patients with 80–100 per cent lysis developed postphlebitic symptoms, 3 patients died of unrelated causes and 1 patient was lost to follow-up.

In patients randomized to heparin therapy no significant lysis was achieved in any of the 25 patients and only 2 of these patients were found to have asymptomatic legs on follow-up. Two patients in this group died and autopsy confirmed massive pulmonary embolus during treatment.

These data suggest that streptokinase is superior to heparin in the treatment of acute proximal venous thrombosis of less than 1 week's clinical duration especially if the thrombus is largely non-occlusive. It must be stressed that in order to avoid the bleeding complications of thrombolytic therapy, streptokinase must not be used within 10 days of major surgery, or even longer after vascular, neurosurgical or eye operations.

THE management of deep venous thrombosis and its complications remains a controversial problem. Pulmonary embolism represents one of the leading causes of death in hospital and nearly all patients with symptomatic iliofemoral thrombosis will eventually develop the postphlebitic syndrome characterized by oedema, eczema, ulceration and occasionally venous claudication (Bauer, 1942).

The goal of therapy in the treatment of acute deep venous thrombosis is the prevention of pulmonary embolism, the dissolution of all thrombus and the preservation of the venous valves, thus preventing subsequent ambulatory venous hypertension. Heparin appears to be of benefit in reducing the incidence of embolism (Barritt and Jordan, 1960), but it appears to be of little value in reducing the incidence of the postphlebitic syndrome.

The operation of venous thrombectomy for the treatment of iliofemoral thrombosis was first described by Leriche in 1928. Haller (1961) and Mavor (1969) demonstrated encouraging results, but long term follow-up (Lansing and Davis, 1968; Johansson et al., 1973) has shown that the incidence of the postphlebitic syndrome is not reduced, that there is a high incidence of reocclusion and that the procedure is associated with a significant morbidity and mortality.

During the past decade several reports describing the use of thrombolytic therapy for the treatment of deep venous thrombosis have been published (Kakkar et al., 1969; Tsapogas et al., 1973; Porter et al., 1975; Arnesen et al., 1978). Common to all is the significant lysis obtained in patients treated with streptokinase; however, little information is available regarding the incidence of long term rethrombosis, morbidity and incidence of pulmonary embolism during treatment. For this reason it was decided to mount a prospective, controlled, randomized, comparative study to compare conventional full dose heparin and streptokinase (Kabikinase—manufacturer's recommended dosage) in the treatment of acute deep venous thrombosis.

Patients and methods

Patients with a clinical history of deep venous thrombosis of less than 8 days' duration were submitted to bilateral ascending phlebography. If this revealed extensive proximal vein thrombosis (extension beyond the axial veins of the calf or forearm) and there was no contraindication to thrombolytic therapy, these patients were eligible for entry into the study and were randomized at this stage to one of the two forms of therapy.

Contraindications to thrombolytic therapy (and hence entry into the study) included any surgery within 7 days (neurosurgical operations within 2 months), pregnancy, menstruation, haemorrhagic diatheses, diastolic blood pressure of 110 mmHg, suspected or known bleeding lesions, a cerebrovascular accident within the preceding 6 months, a recent streptococcal infection, previous streptokinase therapy within 6 months and severe liver or renal disease.

Phlebography

Bilateral ascending phlebography was performed before treatment by the method described by Rabinov and Paulin (1972) and this was repeated on the fifth or sixth day after admission. All radiographs were assessed on a blind basis.

Assessment

On admission to the trial, a detailed proforma was completed for each patient. The patients' legs were examined daily both clinically and by Doppler ultrasound using the methods and criteria of Evans and Cockett (1969). The appearance of symptoms such as chills, rigors, nausea and vomiting was recorded and the frequency of minor and major bleeding episodes was noted.

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Diagnosis of pulmonary embolism during therapy

After admission to the study patients underwent spirometry before and after bronchodilators, posteroanterior and lateral chest radiography and, in most cases, a four-view perfusion lung scan ($^{99}Tc^{m}$ MAA Nuclear Chicago Pho-Gamma III camera). Wherever possible, the chest radiograph and perfusion lung scan were repeated on the seventh post-admission day. These results were blindly assessed and a numerical score recorded which reflected the degree of confidence with which a perfusion defect was regarded as representing a pulmonary embolus (Immelman et al., 1979).

Laboratory tests

A full blood count and serum urea were obtained before therapy and the haemoglobin estimation was repeated after the fifth day of treatment. The platelet count, prothrombin index, serum fibrinogen, fibrin degradation products and thrombin clotting time estimations were performed before, during and after the infusion of streptokinase. Because this trial was studying a standard dosage schedule of streptokinase no adjustment was made according to the above results.

Administration of drugs

Streptokinase (*Kabikinase*): A loading dose of 600 000 units of streptokinase was given by infusion over a period of 30 min. Thereafter a constant infusion of streptokinase at a rate of 100 000 units hourly was given for 3 days by means of a

Table I: SEX, AGE, DURATION OF SYMPTOMS AND DISTRIBUTION OF THROMBI IN THE TWO TREATMENT GROUPS

	Heparin	Streptokinase
Males	7	10
Females	18	16
Average age (yr)	51	48
Average clinical history (d)	3	3
Bilateral thrombosis	5 (20%)	4 (15%)
Axillary vein thrombosis	0	2
Iliofemoral thrombosis	1	2
Iliofemoropopliteal thrombosis	15	13
Femoropopliteal thrombosis	9	9

Table II: PATIENTS TREATED WITH STREPTOKINASE (26 CASES)

Description of thrombus	Duration of symptoms (d)	% lysis at 5 days	3 mth venogram	Complications	Follow-up
Occlusive					
IFP	1	0	—	—	2 yr oedema, aching, venous claudication
	4	0	—	Prescription stopped day 1: anaphylaxis	4 mth carcinoma colon
	3	0	No change	Prescription stopped day 3: bleeding	1 yr oedema, aching
	3	0	No change	—	2 yr oedema, aching
	2	15	No change	—	2 yr oedema, aching, venous claudication
	3	20	No change	—	2 yr oedema, aching
	1*	30	—	—	1 yr oedema
	5	40	No change	—	Lost
	3	80	—	—	4 mth Hodgkin's disease, septicaemia†
	1	90	100	—	1 yr asymptomatic
	1	90	100	—	3 mth asymptomatic, then lost
IF	7	100	No change	Asymptomatic PE on prescription	6 mth asymptomatic
FP	1	0	No change	Prescription stopped day 3: bleeding	2 yr oedema, aching
	2	80	No change	—	18 mth asymptomatic
	2	90	No change	—	18 mth asymptomatic
	4	100	No change	—	6 mth asymptomatic, 18 mth malignant melanoma†
Ax.	3	100	No change	—	9th asymptomatic
	4	100	No change	—	10 mth asymptomatic
Non-occlusive					
IFP	2	100	—	—	3 mth asymptomatic 14 wk†
	6	95	Rethrombosed popliteal vein	—	2 yr asymptomatic
	7	100	Rethrombosed superficial femoral vein	—	1 yr oedema
FP	1	95	Refused	—	2 yr asymptomatic
	2	100	No change	—	2 yr asymptomatic
	2	100	No change	—	18 mth asymptomatic
	3	100	No change	—	6 mth asymptomatic
	6	80	100	—	1 yr asymptomatic

IFP, Iliofemoropopliteal; IF, iliofemoral; FP, femoropopliteal; Ax., axillary.
* Phlegmasia caerulea dolens.
† Died.

constant infusion pump. On completion of the streptokinase, full dose heparin was commenced and maintained for 4 days, the dosage being adjusted to maintain the Lee–White clotting time to at least two and a half to three times normal.

Heparin: Upon diagnosis, 10 000 units of heparin were given immediately by intravenous injection. Thereafter 10 000 units were given intravenously 6-hourly using a constant infusion pump. The dose was adjusted to maintain the clotting time to at least two and a half to three times normal. Treatment was continued for 7 days.

Other drugs: Patients received 100 mg of hydrocortisone 15 min before the administration of the first dose of streptokinase. This was repeated 6-hourly for the duration of streptokinase infusion. Warfarin 20 mg was given as a loading dose to both groups of patients 36 h before heparin therapy was terminated and warfarin was continued for at least 8 weeks with the dose being adjusted to maintain the prothrombin index at 40–60 per cent.

Other measures

All patients were confined to bed during treatment. The foot of the bed was raised by 60 cm and elastic support to the legs was provided (TED Anti-embolism Stockings: Kendall Co.). An intravenous catheter was inserted into the median cubital vein before therapy was commenced and this was maintained for the entire 7 days of intravenous therapy. No intramuscular injections were given during treatment.

Follow-up

During follow-up the sequelae of deep vein thrombosis which were evaluated included aching, oedema, varicose veins, venous claudication and skin changes including ulceration.

Ascending phlebography was performed 3 months after admission to the trial and was repeated at 12 months unless the patient was entirely asymptomatic. Cine-phlebography was performed 3 months after streptokinase in 9 patients.

Results

A total of 51 patients was included in this study: 26 received streptokinase while 25 received heparin. The two groups were well matched for age, sex, duration of symptoms and distribution of thrombi (*Table I*).

Streptokinase group (Table II)

In 3 of the 26 patients treated with streptokinase therapy was terminated early because of complications (*Table III*). In 2 of these patients, both of whom had undergone major abdominal surgery (cholecystectomy and sigmoid colectomy) 7 days previously, life-threatening bleeding occurred. In the remaining patient streptokinase was terminated because of a hyperpyrexial response. This latter patient developed a pyrexia of 40 °C during the first 15 min of therapy and the infusion was stopped and an anti-histamine administered. This event occurred early in the trial; however, it is possible that had it occurred later, when more experience had been gained, treatment would not have been stopped. None of these 3 patients showed lysis on the 5-day phlebogram. A further patient completed the full course of streptokinase but developed a large wound haematoma within the first 12 h of subsequent heparin therapy and 2 patients developed a pyrexia exceeding 39 °C while on therapy (*Table III*).

Table III: COMPLICATIONS OF TREATMENT IN THE TWO GROUPS

	Heparin	Streptokinase
Severe allergic response	0	1
Bleeding >1500 ml	0	2
Pyrexia >39 °C	0	3
Wound haematoma	0	1

Table IV: DEATHS IN THE TWO GROUPS

Heparin	Streptokinase
PE on sixth day of heparin (clotting time 16 min)*	Carcinoma colon 4 mth
PE on sixth day of warfarin (prothrombin index 27 %)*	Malignant melanoma 3 mth
Pneumonia 8 mth	Malignant melanoma 9 mth
Carcinoma pancreas 10 mth	Hodgkin's/septicaemia 4 mth*

* Post-mortem examination
PE, Pulmonary embolus.

Of the 23 patients completing therapy, complete lysis of all visible thrombus was achieved in 9 patients, 90 per cent lysis in 5 and 80 per cent lysis in 3. Thus 17 (74 per cent) of the patients achieved clot lysis of between 80 and 100 per cent. One patient with phlegmasia caerulea dolens and peripheral venous gangrene showed a remarkably rapid clinical improvement, although there was only 30 per cent lysis of the deep system (Elliot et al., 1979). In the remaining 5 patients there was no significant lysis.

One patient, a 23-year-old woman, developed asymptomatic pulmonary emboli during treatment. She had initially presented with a 7-day history of pain in the left leg and was found to have an occlusive thrombus of the left iliofemoral segment (*Fig.* 1). No respiratory symptoms were present, chest X-ray and spirometry were normal, but a pre-treatment perfusion lung scan showed a small defect at the right base (*Fig.* 2). Phlebography on day 6 revealed total lysis of the thrombus (*Fig.* 3) and, although the patient remained otherwise asymptomatic with a clear chest X-ray, the repeat perfusion scan now showed multiple defects (*Fig.* 2). A xenon scan at this time showed normal ventilation of the poorly perfused areas.

Clinical examination at 3 months indicated that 16 out of the 17 patients with 80–100 per cent lysis had asymptomatic legs and on further follow-up to a mean period of 19 months, 12 patients remained asymptomatic while 3 had died of unrelated causes (*Table IV*) and 1 was lost to follow-up (*Table II*).

In contrast, the 9 patients who did not achieve substantial lysis after streptokinase fared less well. After a mean period of 19 months, 5 patients had symptoms of aching and oedema, 2 patients had venous claudication, 1 had died of carcinomatosis (*Table IV*) and one was lost to follow-up (*Table II*).

Phlebography was performed 3 months after therapy in 20 patients. In 2 patients partial rethrombosis had occurred whilst in 3 patients (who previously achieved 80–100 per cent lysis on day 5) the deep veins were shown to be completely clear. Cine-phlebography was performed 3 months after therapy in the 9 patients who had achieved 100 per cent lysis as shown on the 5-day post-treatment phlebogram. Normal valvular function was confirmed in 8 patients. All other patients with either a perfect or near-perfect result on day 5 maintained their good result. In the 9 patients who did not achieve initial substantial lysis (including 3 patients in whom streptokinase therapy was stopped because of complications) phlebography at 3 and in some cases 12 months showed considerable recanalization and collateral development but without restoration of valvular function.

Heparin group

No significant lysis was achieved in any of the 25 patients randomized to heparin therapy as assessed

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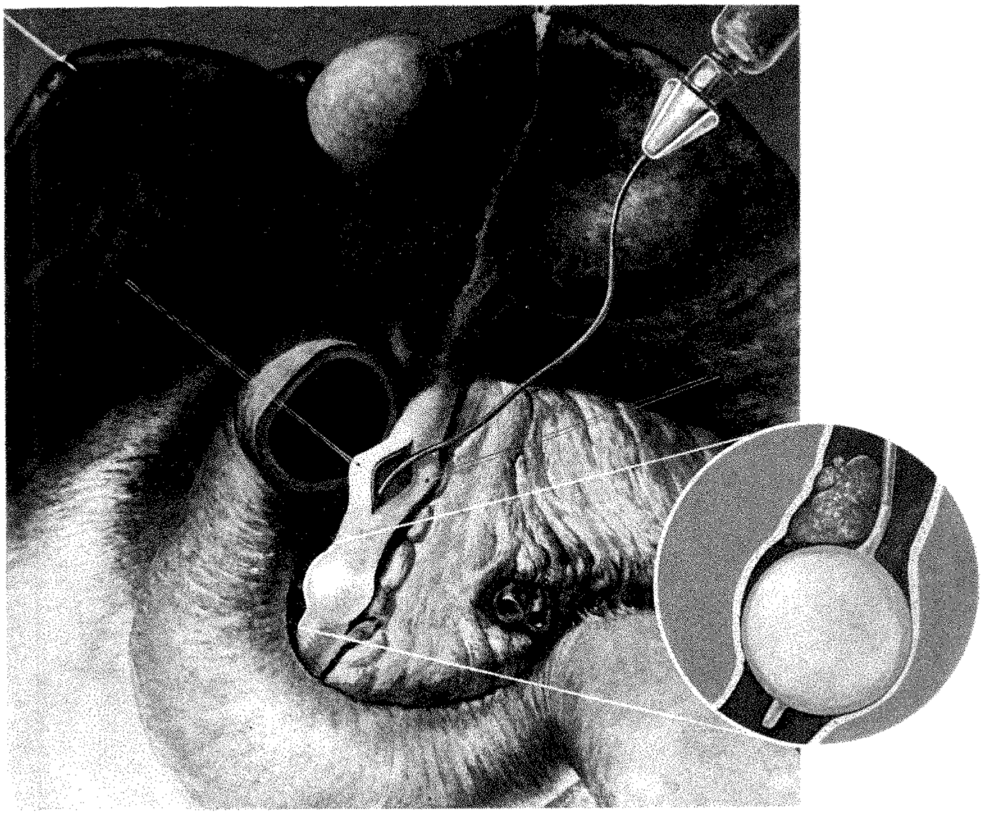

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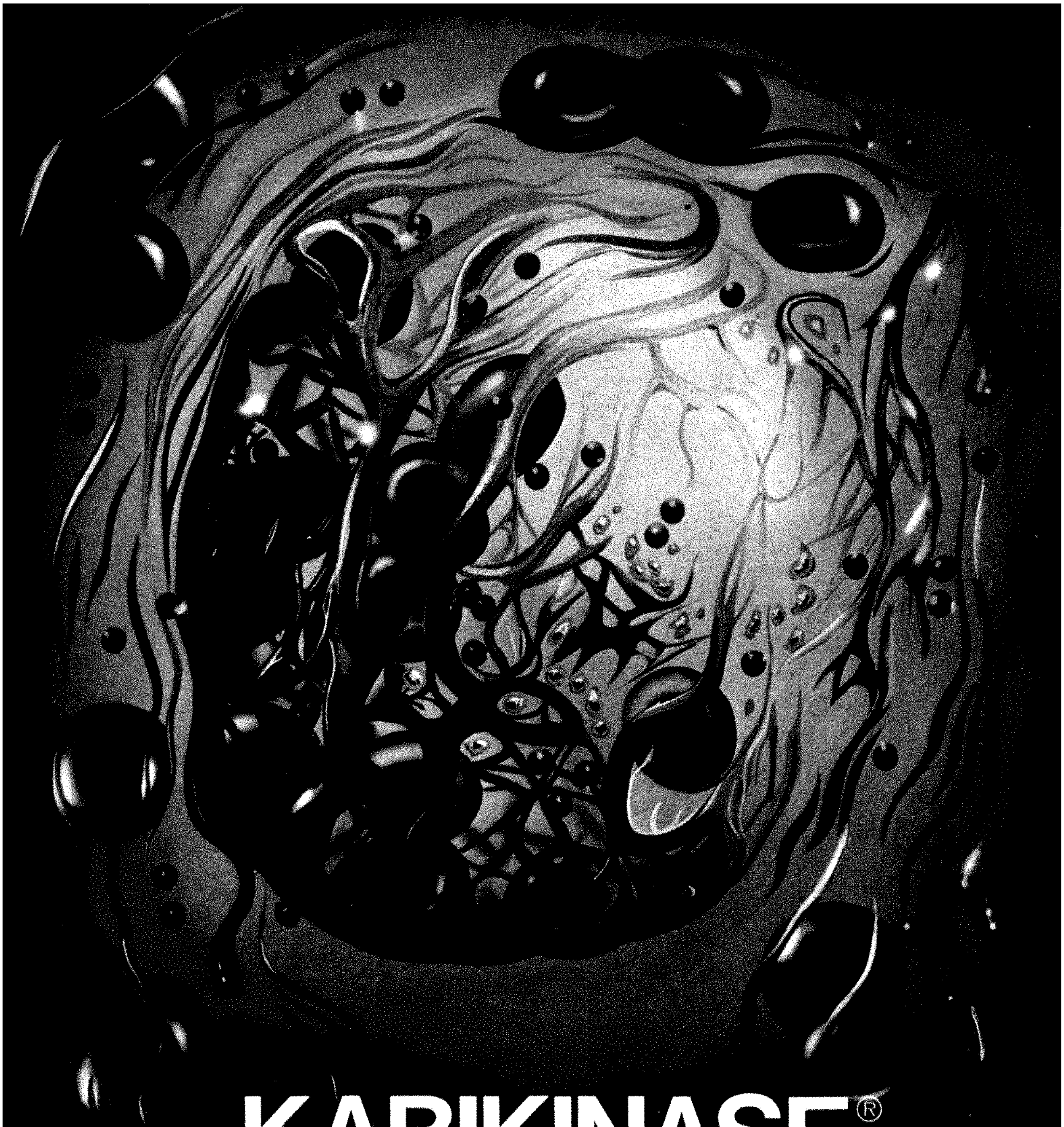

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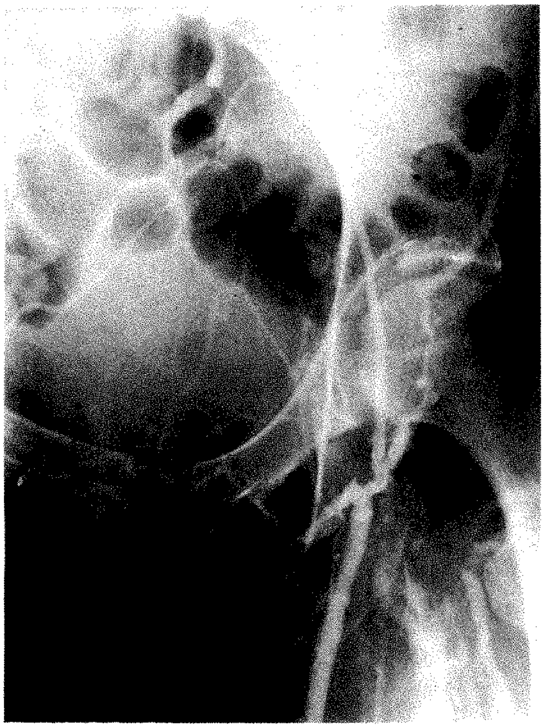

Fig. 1. Pre-treatment phlebogram of left lower limb showing an occlusive thrombus of the iliofemoral venous segment.

by phlebography on day 5. In fact, 2 patients showed further extension of thrombosis. There were no major bleeding problems.

Four patients in this group have died (*Table IV*). Two patients died from massive pulmonary embolism confirmed by autopsy. The first patient died on the sixth day of heparin treatment despite a whole blood clotting time of 16 min. The second patient was admitted with non-occlusive popliteal vein thrombosis: phlebography on day 5 revealed that there had been extension of the thrombosis into the superficial femoral vein (*Fig.* 4). This patient died on the sixth day of warfarin therapy when the prothrombin index was 27 per cent. In both patients autopsy revealed extensive, bilateral occluding thrombus involving either the main pulmonary artery or multiple major tributaries with a variable number of pulmonary infarcts. No other primary cause of death was revealed.

Follow-up of the remaining 21 patients ranged from 6 to 33 months (mean 19 months). Only 2 patients had asymptomatic legs while 1 patient had had bilateral distal amputations following an aortic saddle embolus. All other patients had symptoms of aching and oedema, 4 had venous claudication and 1 patient had developed a venous ulcer. Most patients showed considerable recanalization and collateral development on the third or twelfth month phlebogram but without restoration of any valvular function.

Discussion

It is impossible to determine accurately the magnitude of the disability resulting from the postphlebitic syndrome. As early as 1928 Merz estimated that to the community as a whole the cost of the management of chronic venous ulcers of the leg was equal to the cost of pulmonary tuberculosis. Recently O'Donnell et al. (1977) reviewed 21 patients with acute iliofemoral venous thrombosis and showed that the average patient spent almost US $40 000 on medical expenses during a 10-year period.

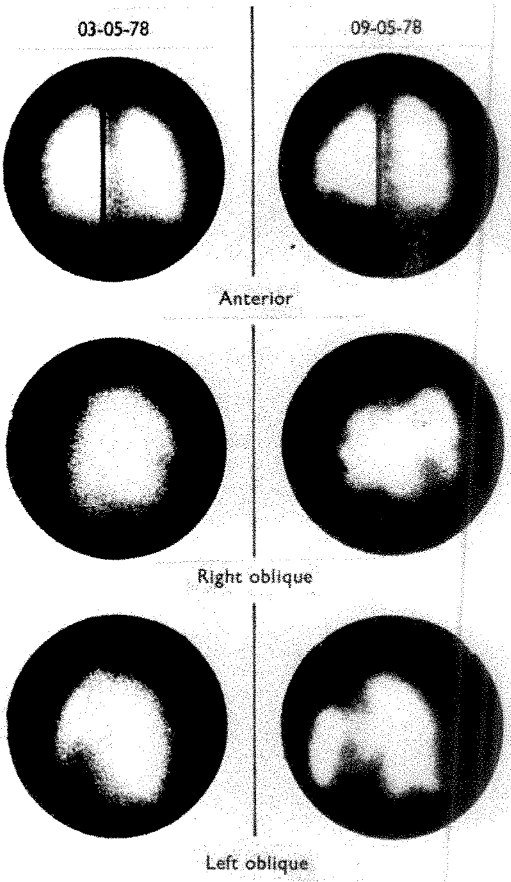

Fig. 2. Pre- and post-treatment pulmonary perfusion scans of a 23-year-old female with iliofemoral venous thrombosis treated with streptokinase. Post-treatment perfusion scan revealed multiple defects with a normal chest X-ray and ventilation scan indicating that an asymptomatic pulmonary embolism had occurred during treatment.

At the present time there is no evidence that thrombolytic therapy will decrease the incidence of pulmonary embolization from an established deep vein thrombosis. Thus the rationale for this form of therapy, which is both expensive and potentially dangerous, is the dissolution of thrombus with the preservation of venous valves and thus the prevention of the postphlebitic syndrome. If this could be proved, the cost of thrombolytic treatment would be fully justified. Significant lysis at the termination of therapy is on its own meaningless unless it can be shown that this clearance can be maintained on long term follow-up.

Previous randomized studies comparing streptokinase with heparin (Kakkar et al., 1969; Tsapogas et al., 1973; Porter et al., 1975; Arnesen et al., 1978) showed that complete lysis with restoration of venous valvular function was found in approximately 30 per

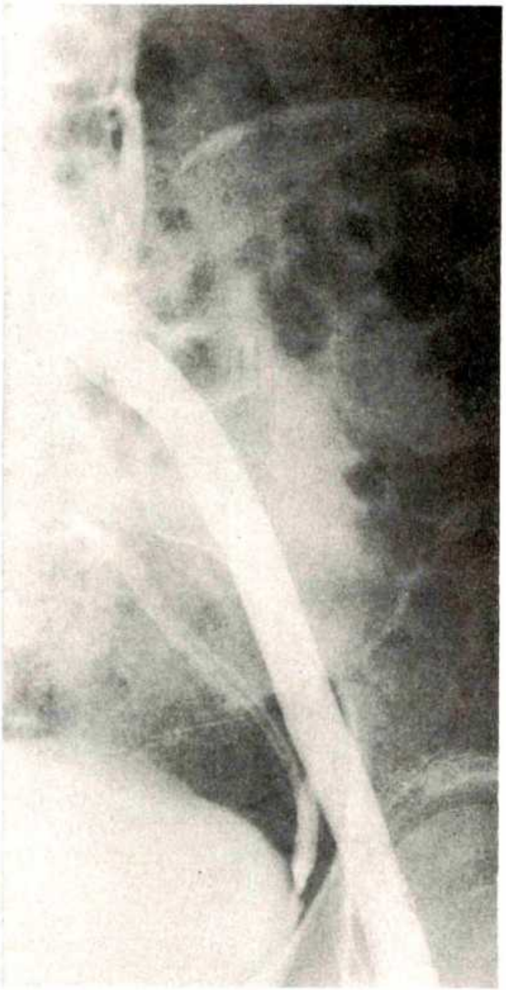

Fig. 3. Phlebogram after streptokinase therapy (day 6) showing complete lysis of the iliofemoral venous segment.

Table V: THERAPEUTIC RESULTS OF STREPTOKINASE AND HEPARIN IN DEEP VENOUS THROMBOSIS

	Heparin	Streptokinase
No. of patients	25	26
Complete (or substantial) lysis (>80%)	0 (0%)	17 (65%)

Table VI: FOLLOW-UP OF HEPARIN/STREPTOKINASE PATIENTS (MEAN 19 MONTHS)

	Heparin	Streptokinase
No. of cases	25	26
Dead/massive pulmonary embolus	2	0
Dead/other causes	2	4
Asymptomatic pulmonary embolus during treatment	0	1
Lost to follow-up	0	2
Asymptomatic patients	2	12
Symptomatic patients	19	8
Venous claudication	4	2
Venous ulceration	1	0

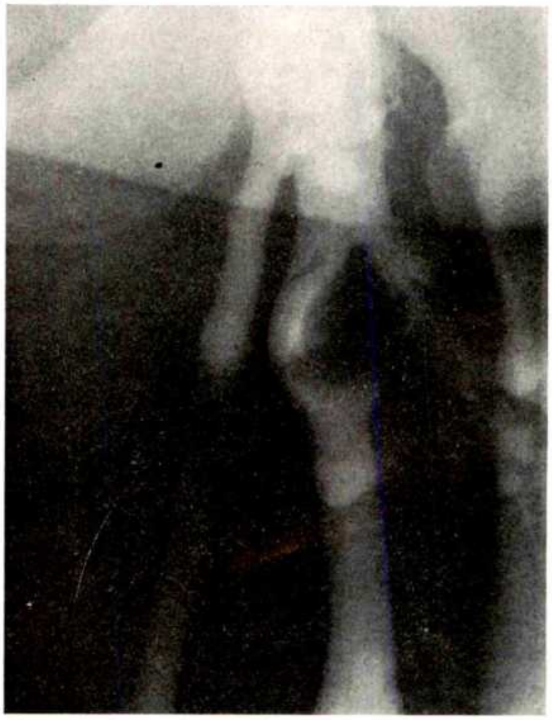

Fig. 4. Phlebogram (day 5) of patient being treated with heparin alone. Extension of thrombosis had occurred with fresh non-occlusive thrombus lying in the superficial femoral vein. Eight days later the patient died of a massive pulmonary embolism confirmed by autopsy.

cent of streptokinase patients, with substantial lysis in a further 65 per cent. In contrast, patients receiving heparin in these studies showed clot lysis of less than 10 per cent on post-treatment phlebography. These results are similar to those of our own study in which we found complete or substantial lysis (80–100 per cent) in two-thirds of our patients receiving streptokinase and in none of the patients receiving heparin (*Table V*).

A review of our streptokinase patients (*Table II*) suggests that the ideal patient for thrombolytic therapy is one with a non-occlusive thrombus and a clinical history of 7 days or less.

In 1968 Browse et al. suggested that occlusive thrombi were not amenable to thrombolytic therapy. However, in 1978 Arnesen et al. stated that they could find no difference in the degree of lysis achieved when treating either occlusive or non-occlusive thrombi. In the present series 8 patients had largely non-occlusive thrombus and all achieved degrees of lysis exceeding 80 per cent as shown on the 5-day phlebogram. In 2 of these patients with a late clinical presentation partial rethrombosis followed initially successful lysis.

In the 18 patients with largely occlusive thrombus 15 completed a full course of streptokinase and 9 of these patients achieved degrees of lysis exceeding 80 per cent on 5-day phlebogram and 8 remained asymptomatic on follow-up. Thus, although the results are a little less impressive for the patient with largely occlusive thrombus, our results indicate that streptokinase therapy should be considered for these patients if the clinical history is less than 7 days.

Follow-up of the two groups in this study reveals a higher incidence of postphlebitic complications in the heparin group commensurate with the absence of lysis in this group (*Table VI*). None of the heparin patients had a normal venous system at 3 months whereas 10 out of 26 streptokinase patients had a completely normal deep venous system.

In the streptokinase group 1 patient developed an asymptomatic pulmonary embolus during treatment. In the heparin group 2 patients died of massive pulmonary emboli while on adequate anticoagulation (*Table IV*).

The frequency and severity of major complications were greater in the group of patients treated with streptokinase (*Table III*). Two of the 3 patients who suffered major haemorrhage had undergone major abdominal surgery 7 days previously while the third had had an operation 20 days earlier. Bleeding complications can on the whole be prevented by careful patient selection, avoidance of thrombolytic therapy in patients within 10 days of major surgery, inserting an adequate intravenous catheter before commencement of therapy and avoiding all invasive procedures during therapy. Minor complications such as a slight pyrexia or bleeding around venepuncture sites were more common in the streptokinase patients than among the heparin-treated patients.

In 2 of the 3 streptokinase patients who suffered major bleeding complications bleeding occurred either during the last few hours of streptokinase therapy or during the first 12 h of subsequent heparin therapy. It is interesting to speculate on the mechanism involved. It is possible that as soon as the streptokinase infusion is stopped, less activator is formed and therefore the level of proactivator plasminogen begins to rise. However, as activator and proactivator plasminogen combine in a ratio of 1 : 9 molecules, it is possible that in this period excessive hyperplasminaemia is occurring with the associated risk of bleeding. Obviously the immediate infusion of heparin, as performed in this study, compounded this problem. We have therefore altered our drug schedule and now wait for approximately 4 h after cessation of the streptokinase infusion, until the thrombin clotting time has decreased to approximately twice the control value, before commencing heparin therapy.

All patients in this study who were treated with streptokinase received a standardized dosage schedule. We agree entirely with the findings of Marder et al. (1977) in that there appeared to be no correlation between the response to streptokinase (assessed by phlebography) and the serum fibrinogen, thrombin clotting time and fibrin degradation levels. The need for strict laboratory control can therefore be questioned because it is time-consuming and involves multiple venepunctures. We would stress, however, that constant clinical control is indispensable and that laboratory tests are required before treatment to detect any serious haemostatic defect and also after treatment to re-establish a base line for heparin therapy.

In conclusion, we feel that streptokinase therapy is the treatment of choice for phlebographically proved extensive thrombi of the deep veins, provided that the clinical history is no longer than 7 days, optimal results being achieved in patients with largely non-occlusive thrombus. Complications can largely be prevented by careful patient selection, close clinical observation and avoidance of all invasive procedures during therapy. Any surgical procedure within 10 days is a direct contraindication to streptokinase therapy.

Acknowledgements

We are extremely grateful to the staff surgeons, physicians and patients who cooperated so wholeheartedly in this study. Expert technical assistance was provided by Mrs G. Shaw, Mrs G. M. Wheeler and Mrs T. Wolfe. Financial assistance obtained from the South African Medical Research Council, the University of Cape Town Staff Research Fund, the Nellie Atkinson Trust and Pharmacal Ethicals is gratefully acknowledged.

References

ARNESEN H., HEILO A., JAKOBSEN E. et al. (1978) A prospective study of streptokinase and heparin in the treatment of deep vein thrombosis. *Acta Med. Scand.* **203**, 457–463.

BARRITT D. W. and JORDAN S. C. (1960) Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet* **1**, 1309–1312.

BAUER G. (1942) Roentgenological and clinical study of the sequels of thrombosis. *Acta Chir. Scand.* **74**, Suppl. pp. 54–61.

BROWSE N. L., LEA THOMAS M. and PIN H. P. (1968) Streptokinase and deep vein thrombosis. *Br. Med. J.* **3**, 717–720.

ELLIOT M. S., IMMELMAN E. J., JEFFREY P. et al. (1979) The role of thrombolytic therapy in the management of phlegmasia caerulea dolens. *Br. J. Surg.* **66**, 422–424.

EVANS D. S. and COCKETT F. B. (1969) Diagnosis of deep vein thrombosis with an ultrasonic Doppler technique. *Br. Med. J.* **2**, 802–804.

HALLER J. A. (1961) Thrombectomy for acute ilio-femoral venous thrombosis. *Arch. Surg.* **83**, 448–457.

IMMELMAN E. J., JEFFREY P., BENATAR S. R. et al. (1979) Failure of low-dose heparin to prevent significant thromboembolic complications in high-risk surgical patients: an interim report of a prospective study. *Br. Med. J.* **1**, 1447–1450.

JOHANSSON E., NORDLANDER S. and ZETTERQUIST S. (1973) Venous thrombectomy in the lower extremity—clinical, phlebographic and plethysmographic evaluation of early and late results. *Acta Chir. Scand.* **139**, 511–516.

KAKKAR V. V., FLANC C., HOWE C. T. et al. (1969) Treatment of deep vein thrombosis. A trial of heparin, streptokinase and arvin. *Br. Med. J.* **1**, 806–810.

LANSING A. M. and DAVIS W. M. (1968) Five-year follow-up study of iliofemoral venous thrombectomy. *Am. Surg.* **168**, 620–628.

MARDER V. J., SOULEN R. L., ATICHARTAKARN V. et al. (1977) Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. *J. Lab. Clin. Med.* **89**, 1018–1029.

MAVOR G. E. (1969) Deep vein thrombosis—surgical management. *Br. Med. J.* **4**, 680–682.

MERZ W. R. (1953) Kontrolle der therapeutischen Heparinkung im Blut bei Thromboseerkrankung. *Schweiz. Med. Wochenschr.* **83**, 407–410.

O'DONNELL T. F., BROWSE N. L., BURNAND K. G. et al. (1977) The socioeconomic effects of an ilio-femoral thrombosis. *J. Surg. Res.* **22**, 483–488.

PORTER J. M., SEAMAN A. J., COMMON H. H. et al. (1975) Comparison of heparin and streptokinase in the treatment of venous thrombosis. *Am. Surg.* **41**, 511–519.

RABINOV K. and PAULIN S. (1972) Roentgen diagnosis of venous thrombosis in the leg. *Arch. Surg.* **104**, 134–144.

TSAPOGAS M. J., PEABODY R. A., WU K. T. et al. (1973) Controlled study of thrombolytic therapy in deep vein thrombosis. *Surgery* **74**, 973–984.

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Anticoagulant activity and operative blood loss after intrapulmonary heparin

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SUMMARY

The safety and efficacy of heparin given by the intrapulmonary route are further assessed in this study. A single dose of heparin (2000 units/kg) was given by intratracheal instillation in dogs and measurements of plasma heparin concentration, whole blood clotting time and partial thromboplastin time made at intervals for 48 h. These values rose progressively and in parallel for 7 h and remained elevated for 48 h.

A series of operations was performed on dogs within 3 h of a single dose of intrapulmonary heparin (1500 units/kg). Operations involving minimal dissection (small bowel resection) and extensive dissection (resection of muscle) were performed in two separate groups. Within each group the animals were randomly given heparin or saline. In the limited dissection group there were no differences in operative blood loss, wound healing, or sequential haemoglobin and haematocrit measurements. In the group subjected to muscle resection there was increased postoperative wound drainage and a slightly greater fall in haemoglobin and haematocrit in those given heparin.

It is concluded that heparin is absorbed from the lung causing significant changes in coagulation parameters. Even with the relatively high dose of 1500 units/kg, operations were performed with minimal hazard. Intrapulmonary heparin may have important clinical applications after further investigation.

STUDIES by Windsor and Freeman (1964), Rosner (1965), Bardana et al. (1969) and Youngchaiyud et al. (1969) demonstrated that heparin given by the intrapulmonary route, in doses similar to those usually given intravenously, caused no significant change in coagulation parameters. The impression—subsequently proved to be erroneous—was thus gained that heparin is not absorbed by the lung. Recent studies by Jaques et al. (1976), Kavanagh and Jaques (1976), Mahadoo (1978) and Wright and Jaques (1979) have shown that a single large dose of intrapulmonary heparin (1500 units/kg) causes a moderate but prolonged hypocoagulable state, lasting from 2 days in dogs to 10 days in humans. Mahadoo (1978) has shown that the heparin is rapidly absorbed from the lung and that it probably exerts its prolonged effect by slow release from a cellular pool throughout the body.

The use of low dose heparin is now firmly established in the prophylaxis of thromboembolic disease and the preliminary studies suggest that the intrapulmonary route may be effective and convenient. This study was designed to measure the effect of intrapulmonary heparin on coagulation parameters and plasma heparin levels, and to assess the safety of intrapulmonary heparin when administration of the drug is followed by an operation.

Materials and methods

Anticoagulant effects of intrapulmonary heparin

Five dogs with a mean body weight of 26·0±3·4 kg (±1 s.d.) were lightly anaesthetized with intravenous sodium pentobarbitone 15–20 mg/kg. An endotracheal tube was inserted and a soft catheter then passed through the tube into a major bronchus. Sodium heparin, 2000 units/kg, was injected through the catheter and flushed with 2 ml of saline. Commercial porcine mucosal heparin was used in a concentration of 10 000 units/ml. The volume administered was therefore around 5 ml and in no case was any of the heparin or saline returned through the endotracheal tube after removal of the catheter. The dog was then extubated and allowed to regain consciousness.

Plasma heparin concentration was measured by the thrombin clotting time assay described by Penner (1974). Whole blood clotting time was measured by a standard modification of the Lee and White (1913) technique. One millilitre of blood is placed in each of three glass tubes of internal diameter 8 mm in a water bath at 37 °C. The first tube is gently tilted at 30-s intervals until the blood fails to flow up the side. The second and third tubes are sequentially handled in the same manner, and the end-point taken to be clotting in the third tube. In 30 preliminary experiments in dogs, this technique gave a control whole blood clotting time of 5·1±0·4 min (mean±1 s.d.). The activated partial thromboplastin time was measured by the Lancer coagulizer, using a photo-optical clot detection system. These measurements were made after induction of anaesthesia, and 3, 5, 7, 24 and 48 h after the heparin was administered.

Perioperative blood loss after intrapulmonary heparin

Two operations on dogs were chosen to assess the effect of intrapulmonary heparin on blood loss. Small bowel resection was selected as an operation that would usually be expected to cause minimal blood loss and a partial resection of sacrospinalis muscle as one that would cause significant haemorrhage.

Group A consisted of 10 dogs of body weight 21·8±2·9 kg. Each was anaesthetized with 20–25 mg/kg of sodium pentobarbitone, intubated and ventilated with a Harvard pump. Venous samples were taken for haemoglobin and haematocrit measurements. Using a random numbers table, half of the group received 1500 units/kg of heparin by the intrapulmonary route as described above and the other half received an equivalent volume of saline only. The surgeon (C. J. W.) was not aware which animals had received heparin and which saline until the entire series was complete. Midline laparotomy was performed and a 20-cm segment of distal small bowel excised with end-to-end anastomosis using a standard two-layer technique. The incision was closed without drainage and the animal was allowed to recover with food and water ad libitum. All operative blood loss was carefully sponged and measured. The haemoglobin and haematocrit were measured daily for 5 days and then post mortem examination was performed after a lethal intravenous dose of sodium thiopentone.

In group B there were 20 dogs of body weight 23·8±3·6 kg. Ten received heparin 1500 units/kg and 10 saline as described above. The experimental procedure was as in group A, with the following modifications. Each dog was placed prone on the operating table and approximately 50 g of sacrospinalis muscle on the right side were excised through a 15-cm skin incision. Multiple bleeding points were ligated as they were encountered. A closed suction tube drain was left in the wound, brought out through a stab incision and the skin wound sutured. The mass of muscle excised was weighed and the suction drain blood loss measured daily for 5 days. Measurements of operative blood loss, and of haemoglobin and haematocrit, were made each day as in group A.

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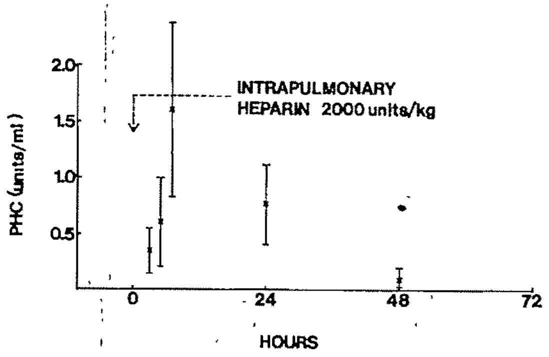

Fig. 1. Plasma heparin concentrations after intratracheal instillation of 2000 units/kg. Mean values±1 standard deviation.

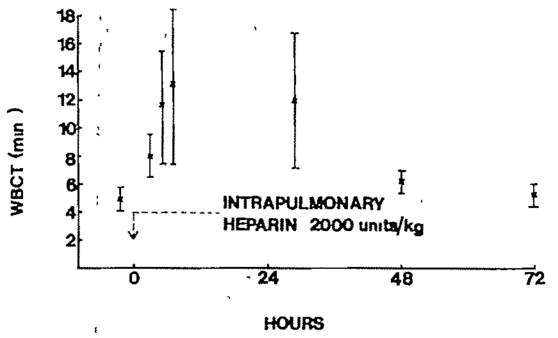

Fig. 2. Whole blood clotting time after intratracheal instillation of 2000 units/kg of heparin. Mean values±1 standard deviation.

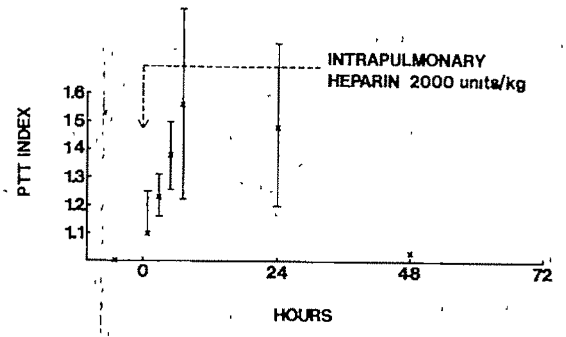

Fig. 3. The partial thromboplastin time is expressed as an index: each sample value divided by the control value. Mean values±1 standard deviation.

No blood was transfused in any of the experiments, but during the operative procedure an intravenous infusion of 500 ml saline was given.

Statistical methods

The means and standard deviations were calculated for each group of samples and group A was compared with group B by the Student *t* test for unpaired data. Measurements made at different times within each group were compared by the Student *t* test for paired data.

Results

Anticoagulant effects

The plasma heparin concentration was 0·34±0·2 units/ml 3 h after administration of intrapulmonary heparin and rose to a peak of 1·61±0·86 units/ml at 7 h. *Fig.* 1 shows that the variation of individual samples was wide, but that significant amounts of heparin were still present in the plasma 24 and 48 h after administration.

Table I: MEASUREMENTS RELATING TO PERIOPERATIVE BLOOD LOSS IN GROUP A

	Saline ($n=5$)		Heparin ($n=5$)
Operative blood loss (ml)	79±46	n.s.	66±44
Haemoglobin (g/dl)			
Control	13·3±1·5		13·7±1·5
24 h	13·7±1·4	n.s.	13·9±1·4
48 h	13·6±1·4	n.s.	13·6±1·3
Haematocrit (%)			
Control	41±5		43±5
24 h	43±5	n.s.	45±5
48 h	44±4	n.s.	43±6

Values given as mean±1 standard deviation.
Not significant: $P>0{\cdot}2$.

Table II: MEASUREMENTS RELATING TO PERIOPERATIVE BLOOD LOSS IN GROUP B

	Saline ($n=10$)		Heparin ($n=10$)
Weight of muscle excised (g)	50·6±12·3	n.s.	52·3±13·5
Operative blood loss (ml)	140±82	n.s.	116±70
Postoperative wound drainage (ml)	138±160	$P<0{\cdot}02$	465±411
Haemoglobin (g/dl)			
Control	14·0±1·0		13·2±1·4
24 h	13·9±2·1	n.s.	13·0±1·6
48 h	13·1±1·9	$0{\cdot}05<P<0{\cdot}1$	11·5±2·6
Haematocrit (%)			
Control	43±3		41±4
24 h	44±7	n.s.	41±5
48 h	41±6	$0{\cdot}1<P<0{\cdot}2$	37±8

Values given as mean±1 standard deviation.
Not significant: $P>0{\cdot}2$.

The whole blood clotting time (*Fig.* 2) rose progressively for 7 h and at 24 h was still more than twice the control level. The 48 h level (6·1±0·4 min) remained slightly but significantly higher than the control (4·9±0·4 min, $P<0{\cdot}025$).

The changes in the partial thromboplastin time were small (*Fig.* 3) but they followed a similar pattern to that seen for the plasma heparin concentration and the whole blood clotting time. The control value was defined as unity and subsequent measurements expressed as the ratio of sample to control.

Perioperative blood loss

Group A: Small bowel resection: No postoperative problems were encountered. The wounds healed by primary intention and the animals were fully active by the third postoperative day, with no observable difference between those given saline and those given heparin. The blood loss during operation and the sequential haemoglobin and haematocrit measurements are shown in *Table I.* Blood loss was minimal, the haemoglobin and haematocrit did not change and there were no differences between the heparin-treated and control groups for any of the parameters measured.

Group B: Muscle resection: The results are displayed in *Table II.* The amount of muscle resected and the blood loss during operation were similar in the heparin-treated and control animals, but the postoperative drainage was significantly higher after intrapulmonary heparin. The large standard deviations reflect the fact that individual measurements of total wound drainage over 5 days ranged from 20 ml to 563 ml and from 20 ml to 985 ml in animals given saline and heparin respectively. In the heparin-treated group the haemoglobin and haematocrit levels revealed a definite downward trend by 48 h, but because of wide individual variations the differences were not significant. Healing of the skin wound was uneventful in all animals.

Discussion

Rediscovery of the intrapulmonary route for heparin

The doses of heparin given to patients via the lung by Windsor and Freeman (1964), Rosner (1965), Bardana et al. (1969) and Youngchaiyud et al. (1969) were in the range of 10 000–40 000 units. The changes in the whole blood clotting time were so slight that the intrapulmonary route was rejected as a practical method of heparinization, as it was understood that a therapeutic effect required demonstrable anticoagulant activity. The realization that low doses of heparin, 5000 units subcutaneously every 8 or 12 h, are sufficient to inhibit activated factor $\bar{X}$ (Biggs et al., 1970) and the subsequent overwhelming evidence that low dose heparin markedly reduces the incidence of postoperative thromboembolic disease (Kakkar et al., 1971; Scottish Study, 1974; Kakkar, 1975; Venous Thrombosis Clinical Study Group, 1975) have led to widespread acceptance of the technique in surgical practice.

The efficacy of heparin in low doses also led to a re-evaluation in this laboratory of the intrapulmonary route of administration. Kavanagh and Jaques (1976) found that a single dose of heparin by intratracheal instillation in dogs (1000–2000 units/kg) caused the whole blood clotting time and the partial thromboplastin time to rise for 24–48 h, with a dose–response correlation. Jaques et al. (1976) reported the anticoagulant effects of intrapulmonary heparin in dogs, mice, rats and human volunteers. In all species, a single large dose caused a moderate but prolonged hypocoagulable state lasting from 2 days in dogs to 10 days in man. Intrapulmonary heparin causes no change in lung function or histology (Wright and Jaques, 1979) and no adverse effects were detectable either clinically or radiologically in the human volunteers.

The cellular pool hypothesis

Mahadoo (1978) found that in rats given tritiated heparin by intratracheal instillation, 40 per cent of the administered dose had left the lung 1½ h later and after 24 h only 10 per cent remained. The heparin was found to be taken up by the lung lymphatics, capillaries and alveolar macrophages. It has also been shown that there is a marked arteriovenous difference in plasma heparin concentration and that vascular endothelium takes up heparin against a huge concentration gradient (Hiebert and Jaques, 1976). This work has led to the hypothesis that heparin is distributed throughout the body from the lung and is then slowly released back into the circulation from this cellular pool to cause the prolonged moderate hypocoagulable state which is observed. This hypothesis is currently under critical investigation.

The safety of intrapulmonary heparin

This study demonstrates that a single large dose of heparin by intratracheal instillation in the dog (equivalent to 140 000 units in a 70-kg man) causes significant elevation of the whole blood clotting time and partial thromboplastin time for 48 h. *Figs.* 1–3 show that these changes run in parallel with the plasma heparin concentration. Such a high dose would not be required for a prophylactic regimen but a dose only slightly lower (1500 units/kg) was chosen for the experiments to assess blood loss during operations performed after intrapulmonary heparin. In the 'minimal dissection' operation, the heparin had no detectable effects (*Table I*), but in the 'major dissection' procedure postoperative drainage of blood from the wound was increased (*Table II*). This study did not permit the wide individual variations of postoperative blood loss to be correlated with plasma heparin concentrations as the two factors were measured in different experiments. There was no increased bleeding during the operations, which were all performed within 3 h of heparin administration. The increased postoperative wound haemorrhage may reflect the relatively high plasma heparin concentrations found 7–24 h later. It should be noted, however, that the muscle resection operation described here is the type of procedure in which many surgeons would consider low dose heparin therapy to be contraindicated (Blaisdell, 1978). The subcutaneous low dose heparin regimen is known to cause a small but significant increase in perioperative blood loss and it is interesting to note that the main problem is increased postoperative wound drainage (Allen et al., 1978).

Clinical relevance of intrapulmonary heparin

The experimental work suggests that intrapulmonary heparin may be useful in clinical practice. The subcutaneous low dose heparin regimen requires twice daily injections for 5–7 days with the attendant risks of dispensing errors. A single intrapulmonary dose may provide the moderate level of hypocoagulability for the length of time which is required for the prophylaxis of thromboembolic disease. The first clinical study to establish the dose–response relationship for intrapulmonary heparin in patients is now in progress. Further work must elucidate the role of the cellular reservoir in the prolonged effects of intrapulmonary heparin and any species differences in response. A long term toxicity study involving the administration of heparin into the lung twice weekly is also underway. Depending upon the results of these studies a multicentric clinical trial of intrapulmonary heparin in the prophylaxis of thromboembolic disease in surgical patients will be conducted.

Conclusions

This study confirms that heparin is absorbed when given via the lung in dogs, causing a significant hypocoagulable state with significant levels of heparin in the plasma for at least 48 h. Operations may be performed safely in the dog after 1500 units/kg of intrapulmonary heparin, but increased wound bleeding occurs if major tissue dissection is involved. The intrapulmonary route for heparin administration merits further investigation as a possible means of achieving low dose heparinization.

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References

ALLEN N. H., JENKINS J. D. and SMART C. J. (1978) Surgical haemorrhage in patients given subcutaneous heparin as prophylaxis against thromboembolism. *Br. Med. J.* **1**, 1326.

BARDANA E. J., EDWARDS M. J. and PIROFSKY B. (1969) Heparin as treatment for bronchospasm of asthma. *Ann. Allergy* **27**, 108–113.

BIGGS R., DENSON K. W., AKMAN N. et al. (1970) Antithrombin III, antifactor Xa and heparin. *Br. J. Haematol.* **19**, 283–305.

BLAISDELL F. W. (1978) Prevention of deep vein thrombosis. *Surgery* **83**, 243–244.

HIEBERT L. M. and JAQUES L. B. (1976) The observation of heparin on endothelium after injection. *Thromb. Res.* **8**, 195–204.

JAQUES L. B., MAHADOO J. and KAVANAGH L. W. (1976) Intrapulmonary heparin. A new procedure for anticoagulant therapy. *Lancet* **2**, 1157–1161.

KAKKAR V. V. (1975) Prevention of fatal postoperative pulmonary embolism by low doses of heparin—an international multicentre trial. *Lancet* **2**, 45–51.

KAKKAR V. V., NICOLAIDES A. N., FIELD E. S. et al. (1971) Low doses of heparin in prevention of deep vein thrombosis. *Lancet* **2**, 669–671.

KAVANAGH L. W. and JAQUES L. B. (1976) A new route of heparin administration—the lung. *Arzneim. Forsch.* **26**, 389–392.

LEE R. I. and WHITE P. D. (1913) A clinical study of the coagulation time of blood. *Am. J. Med. Sci.* **145**, 495–503.

MAHADOO J. (1978) Pulmonary administration of heparin. PhD Thesis, University of Saskatchewan.

PENNER J. A. (1974) Experience with a thrombin clotting time assay for measuring heparin activity. *Am. J. Clin. Pathol.* **61**, 645–653.

ROSNER S. W. (1965) Heparin administered as an aerosol. *Vasc. Dis.* **2**, 131–134.

SCOTTISH STUDY (1974) A multi-unit controlled trial: heparin versus dextran in the prevention of deep vein thrombosis. *Lancet* **2**, 118–120.

VENOUS THROMBOSIS CLINICAL STUDY GROUP (1975) Small doses of subcutaneous sodium heparin in the prevention of deep vein thrombosis after elective hip operations. *Br. J. Surg.* **62**, 348–350.

WINDSOR E. and FREEMAN L. (1964) An investigation of routes of administration of heparin other than injection. *Am. J. Med.* **37**, 408–416.

WRIGHT C. J. and JAQUES L. B. (1979) Heparin via the lung. *Can. J. Surg.* **22**, 317–319.

YOUNGCHAIYUD P., KETTEL L. J. and CUGELL D. W. (1969) The effect of heparin aerosols on airway conductance in patients with chronic obstructive pulmonary disease. *Am. Rev. Resp. Dis.* **99**, 449–452.

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Circulating breast tumour antigen-sensitive T lymphocytes in early breast cancer and high risk benign breast disease

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SUMMARY

Levels of circulating T lymphocytes sensitized to breast tumour associated antigens (BTA) were correlated with pathological tumour stage or benign histopathology in preoperative studies of 180 patients by the antigen-stimulated active rosette-forming T cell (AgARFC) assay. Incubation of lymphocytes with allogeneic BTA extracts produced increased AgARFC compared with incubation without BTA. Significant levels of BTA-sensitive T cells were found in 78 per cent of breast cancer patients compared with 23 per cent of patients with benign disease ($P<0.0005$, by χ^2). Over 93 per cent of stage I cancer patients responded to BTA, compared with 69 per cent of stage II patients ($P<0.025$) and 59 per cent of stages III–IV patients ($P<0.005$). Twenty-nine per cent of 42 patients with fibrocystic disease were positive to BTA in contrast to 8 per cent of 25 patients with fibroadenomas. This was a 3·6-fold higher incidence of BTA-sensitive T cells associated with fibrocystic disease than with fibroadenomas, which was in agreement with the increased breast cancer risk rate associated with fibrocystic disease. These findings suggest that the AgARFC assay may detect early malignant change in fibrocystic disease. The AgARFC assay was found to reliably detect early invasive carcinoma.

CELL mediated immunity to breast tumour associated antigens has been investigated as a modality for improved early detection of breast cancer (Farrow, 1970; Herberman, 1976; Order, 1977; Waters, 1978). *In vitro* assays of peripheral blood leucocytes from breast cancer patients have demonstrated proliferation, cell mediated cytotoxicity, migration inhibition and adherence inhibition responses to tumour cells and to soluble tumour associated antigens (Harris and Sinkovics, 1976; Zimmerman et al., 1977). Many of these studies, however, reported either low sensitivity in the detection of malignancies or low specificity in the differentiation of malignant from benign lesions. Recently, we demonstrated T cell mediated immunity to soluble extracts of breast adenocarcinoma by the antigen-stimulated active rosette-forming T cell (AgARFC) assay (Ramey et al., 1979a, b). Peripheral blood T cells from breast cancer patients formed significantly higher percentages of active rosettes with heterologous erythrocytes when incubated with soluble breast tumour associated antigens than when incubated in antigen-free media. We now report the incidence and relationship of peripheral blood T cell responses to breast tumour associated antigens detected by the AgARFC assay, with tumour stage and benign histopathology in patients with clinical breast disease.

Patients and methods

Patients, histopathology and staging

One hundred and eighty inpatients at St Luke's Hospital Center were assayed for circulating T lymphocyte reactivity to soluble breast adenocarcinoma-associated antigens by the AgARFC assay. Heparinized venous blood samples drawn before biopsy or operative manipulation of breast lesions were obtained from 164 women with clinical breast disease. Following surgery the patients were classified according to clinical findings in the medical records and pathological diagnoses were obtained from the routine surgical reports of the Department of Pathology. Patients with mammary carcinomas were classified according to the post-surgical treatment–pathological staging modification of the TNM staging system (American Joint Committee for Cancer Staging and End-Results Reporting, 1977). Patients with benign mastopathy were grouped according to the dominant lesion of the biopsy specimen: (*a*) fibrocystic disease, (*b*) fibroadenoma, (*c*) periductular or perivascular inflammation and (*d*) other benign lesions (including fibrosis, ductal ectasia, ductal or lobular hyperplasia and intraductal papilloma). Sixteen patients with non-mammary carcinomas of a variety of organs were also assayed preoperatively for lymphocyte activity to breast tumour associated antigens. Patients who had received radiation therapy or immunosuppressive drugs, or who had a past history of treated breast carcinoma were not included in this study.

Preparation of breast tumour associated and histocompatibility antigen extracts

Soluble breast tumour associated antigens (BTA) were prepared from fresh tumour tissue (histologically well-differentiated adenocarcinoma) obtained from two radical mastectomy specimens by extraction techniques which have been described previously (Ramey et al., 1979b). In brief, soluble antigen preparations of each tumour (designated BTA_1 and BTA_2) were made by hypertonic potassium chloride extraction of homogenates of minced tumour tissue (2 g wet tumour per 2 ml of 3 M KCl solution) at 4 °C for 16 h. Extracts were ultracentrifuged at 16 000 *g* for 60 min and the supernatants were dialysed three times against 200 volumes of 0·9 per cent NaCl. Dialysates were then centrifuged at 10 000 *g* and the supernatants of the tumour extracts were stored in aliquots at −20 °C. Aliquots were thawed once at room temperature and diluted 1 : 10 in fresh Hank's balanced salt solution (HBSS, Gibco, Long Island, New York) adjusted to pH 7·4, prior to use in the AgARFC assay.

Parallel extracts of peripheral blood lymphocyte histocompatibility antigens (HA) were prepared from heparinized venous blood drawn before mastectomy from the tumour donors (designated HA_1 and HA_2), corresponding to BTA_1 and BTA_2). Lymphocytes were isolated by Ficoll–Hypaque density flotation, washed in HBSS and extracted (10^9 lymphocytes per 20 ml of 3 M KCl) for 16 h at 4 °C (Reisfeld and Kahan, 1970). Ultracentrifugation, dialysis and storage of aliquots were performed as described above. Histocompatibility antigen extracts were diluted to a concentration of 5×10^6 cell-equivalents per ml of HBSS at pH 7·4 before use in the AgARFC assay.

AgARFC, ARFC and TRFC assays

The AgARFC assay for T cell sensitization to soluble antigens has been described in detail elsewhere (Hashim et al., 1977; Ramey et al., 1977; Hashim et al., 1978) and application of this assay to soluble human HA (Burrows et al., 1978) and to

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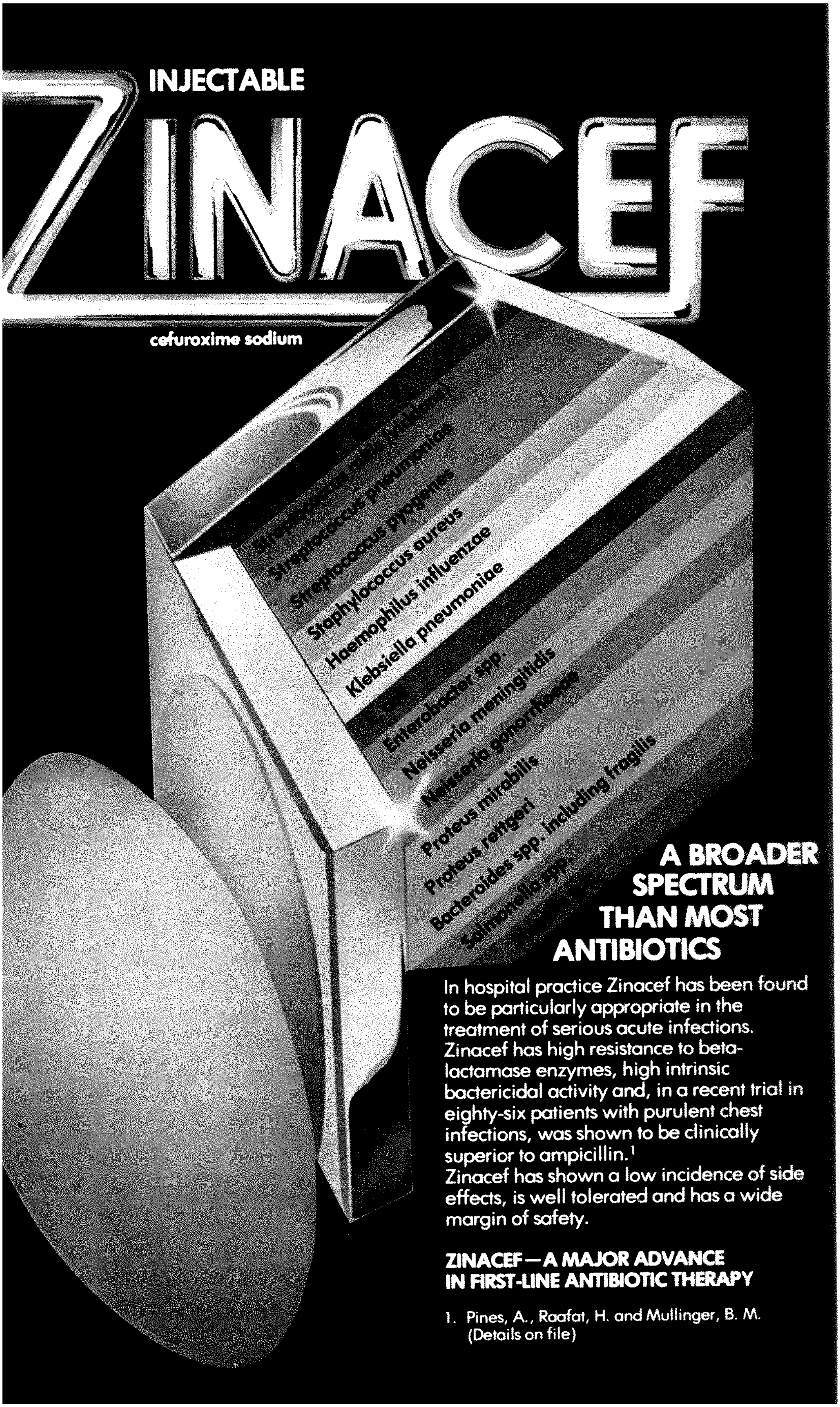

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1. *Cancer Treatment Reports* (1976), **60**, 1431.
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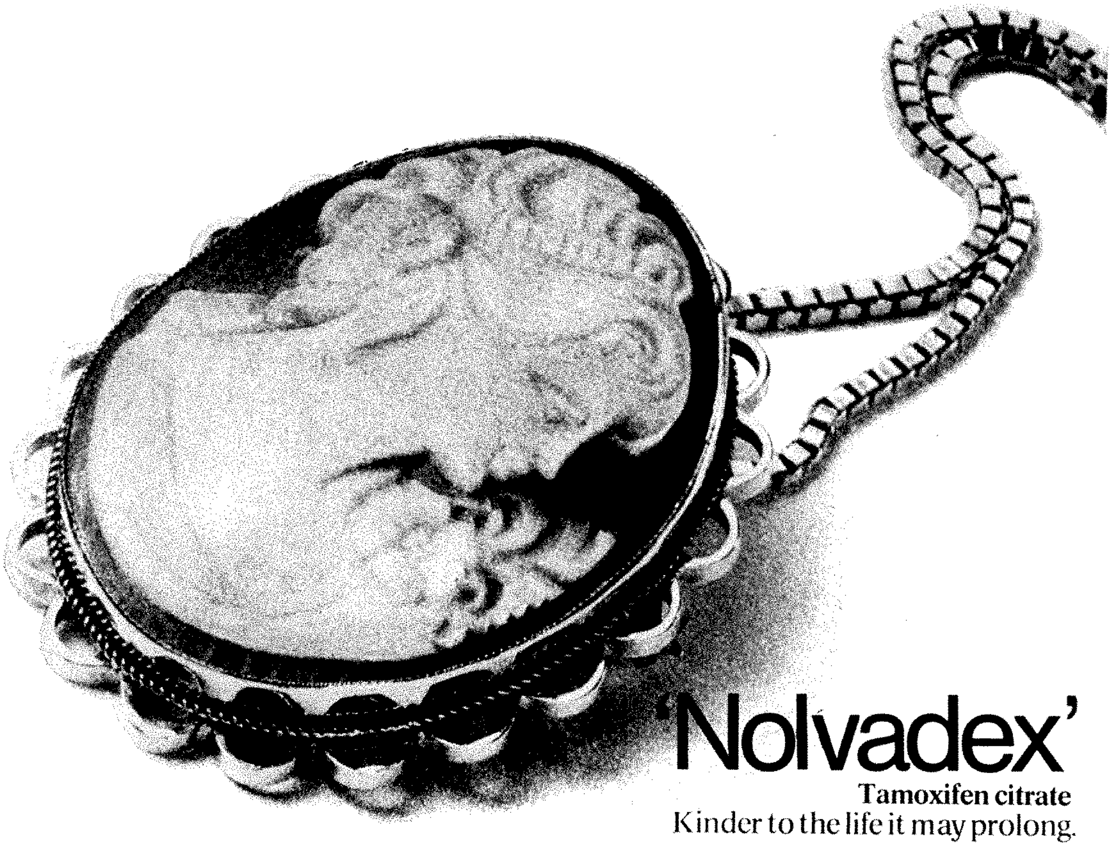

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BTA (Ramey et al., 1979a, b) has been previously reported. In brief, peripheral lymphocytes, isolated from heparinized venous blood samples by Ficoll–Hypaque density flotation, were washed in HBSS, incubated with latex microparticles to label monocytes and suspended in 10 per cent minimal essential medium. Aliquots containing 300 000 lymphocytes per 0·05 ml were incubated in the presence of equal volumes of BTA for 15 min at 37 °C. Incubation was continued for 60 min following addition of 0·05 ml of sheep erythrocyte-adsorbed, gamma globulin-free fetal calf serum. Washed sheep red blood cells (SRBC) (0·05 ml of 0·25 per cent suspension) were added and the mixture was centrifuged at 200 *g* for 5 min. The pellet was gently resuspended and a minimum of 200 lymphocytes were counted on a haemocytometer at 400 times magnification to determine the percentage of rosette-forming lymphocytes (those having three or more adherent SRBC). Non-stimulated active rosette-forming T cells (ARFC) were determined by the same techniques, with 0·05 ml of HBSS substituted for soluble antigen preparation. Total T cell (TRFC) levels were determined with 300 000 lymphocytes in 0·05 ml of HBSS added to 0·05 ml of 2 per cent SRBC and 0·05 ml of adsorbed fetal calf serum, centrifuged at 200 *g* for 5 min and incubated for 60 min at 25 °C. All assays were performed in duplicate.

Nomenclature, calculations and statistical treatment

The subpopulation of peripheral blood lymphocytes that responded to *in vitro* incubation with specific soluble antigen was calculated as the difference between the percentage of antigen-stimulated active rosette-forming T cells (AgARFC, incubated in the presence of antigens) and the non-stimulated active rosette-forming T cells (ARFC, incubated in the absence of antigens). This difference was expressed as the percentage (AgARFC–ARFC). Patients in whom the percentage (AgARFC–ARFC) with either BTA_1 or BTA_2 exceeded 5·5 per cent (the 99·5 per cent upper confidence limit for replicate variation of percentage ARFC determinations for the entire group of patients) and in whom the percentage (AgARFC–ARFC) for corresponding HA was less than 5·5 per cent were designated as testing-positive for circulating BTA-sensitive T cells. All other patients, including those in whom the percentage (AgARFC–ARFC) was greater than 5·5 per cent with BTA *and* with HA, were considered to be negative for sensitization to BTA. All group results were expressed as the mean ± the standard error (s.e.) and group means were analysed by the two-tailed Student's *t* test. Significant differences between the incidences of positive patient responses in each patient group were determined by χ^2 analysis.

Results

Sixty-four of the 164 patients with breast lesions studied preoperatively were found to have breast carcinoma at operation: 31 with stage I, 16 with stage II and 17 with stages III or IV disease. The remaining 100 patients had benign histopathology on biopsy: (*a*) 42 had fibrocystic disease, (*b*) 25 had fibroadenomas, (*c*) 10 had periductal or perivascular inflammation and (*d*) 23 had other benign lesions (fibrosis, ductal ectasia, ductular or lobular hyperplasia, or intraductal papilloma).

Cellular sensitization to BTA in malignant and benign breast disease

Fifty of 64 breast cancer patients (78·1 per cent), all stages, were found by preoperative assay to have greater than 5·5 per cent (AgARFC–ARFC) differences upon incubation with BTA_1 or BTA_2. This incidence of circulating T cells sensitized to BTA in breast cancer patients was significantly higher than the 23·0 per cent of 100 benign mastopathy patients shown to have cellular sensitization to BTA ($P<0{\cdot}0005$, *Table I*). These values were also higher than the 12·5 per cent of non-mammary carcinoma patients responding to BTA ($P<0{\cdot}0005$, *Table II*) in the AgARFC assay.

Table I: CIRCULATING BTA-SENSITIVE T LYMPHOCYTES DETECTED BY THE AgARFC ASSAY IN MALIGNANT AND BENIGN BREAST DISEASE

	Incidence of BTA-sensitive T cells*	
Breast pathology	No. positive	%
Breast carcinoma	50	78·1
Benign mastopathy	23	23·0

$P<0{\cdot}0005$.

* Percentage (AgARFC–ARFC) greater than 5·5 when incubated with BTA.

Table II: BTA-SENSITIVE T CELLS IN NON-MAMMARY CARCINOMA

	Incidence of BTA-sensitive T cells*	
Diagnosis	No. positive	%
Non-mammary carcinoma	2	12·5
Breast carcinoma	50	78·1

$P<0{\cdot}0005$.

* Percentage (AgARFC–ARFC) greater than 5·5 when incubated with BTA.

Table III: CORRELATION OF BREAST CARCINOMA STAGE TO INCIDENCE OF CIRCULATING BTA-SENSITIVE T CELLS

	Patients with BTA*	
Pathological stage	No. positive	%
I	29	93·5[a]
II	11	68·8[b]
III–IV	10	58·8[c]

Significance (χ^2): a *v.* b, $P<0{\cdot}025$; a *v.* c, $P<0{\cdot}005$.

* Percentage (AgARFC–ARFC) greater than 5·5 when incubated with BTA.

Stage–response relationship in breast carcinoma patients

An inverse relationship between the pathological stage of breast carcinoma patients and the incidence of BTA-sensitive T lymphocytes was observed (*Table III*). Twenty-nine of 31 patients (93·5 per cent) with early invasive carcinoma, without axillary nodal metastases (stage I), were found to have BTA-sensitive T lymphocytes. This incidence was significantly higher than the 68·8 per cent of patients with tumour in axillary nodes (stage II, $P<0{\cdot}025$) and the 58·8 per cent of patients with locally advanced or widely metastatic carcinoma (stages III–IV, $P<0{\cdot}005$) positive for BTA-sensitive T cells.

Sensitization to BTA in patients with benign mastopathy

Twenty-three of 100 patients found at operation to have benign breast pathology had greater than 5·5 per cent BTA-sensitive peripheral blood T lymphocytes. Classified according to benign histopathology, 12 of 42 patients with fibrocystic disease (28·6 per cent), 2 of 25 patients with fibroadenomas (8·0 per cent), 5 of 10 patients with predominant periductular or perivascular lymphocytic infiltrates (50·0 per cent), and 5 of 23 patients with other benign conditions (21·7 per cent) were demonstrated to have peripheral blood T cells reactive with either BTA_1 or BTA_2. There were significantly more patients in the fibrocystic disease group reactive to BTA than in the fibroadenoma group ($P<0{\cdot}05$, *Table IV*). Similarly, more of the group of patients with predominant perivascular or periductular infiltrates were shown to have circulating T cell sensitization to BTA extracts than the

Table IV: BTA-SENSITIVE T CELLS IN BENIGN BREAST CONDITIONS OF DIFFERING MALIGNANT POTENTIAL

Benign mastopathy	Patients with BTA* No. positive	%
Fibrocystic disease	12	28·6
Fibroadenoma	2	8·0

Significance (χ^2): $P < 0{\cdot}05$.
* Percentage (AgARFC–ARFC) greater than 5·5 when incubated with BTA.

Table V: BTA-SENSITIVE T CELLS IN OPERABLE BREAST CARCINOMA AND BENIGN BREAST DISEASE

Breast pathology	Patients with BTA* No. positive	%	Significance (χ^2 test)
Stage I or II breast carcinoma	40	85·1	
Fibrocystic disease	12	28·6	$P \ll 0{\cdot}0005$
Fibroadenoma	2	8·0	$P \ll 0{\cdot}0005$
Periductal or perivascular inflammation	5	50·0	$P < 0{\cdot}025$
Other benign conditions†	5	21·7	$P \ll 0{\cdot}0005$

* Percentage (AgARFC–ARFC) greater than 5·5 when incubated with BTA.
† Fibrosis, ductal ectasia, hyperplasia, papillomatosis.

Table VI: PERIPHERAL LYMPHOCYTE COUNTS AND NON-SPECIFIC T CELL SUBPOPULATIONS IN STAGES OF BREAST CARCINOMA

Population	Stage I ($n = 31$)	Stage II ($n = 16$)	Stage III–IV ($n = 17$)
Lymphocytes/mm^3	2114±186	1873±248	2452±510
% TRFC	70·8±1·9*	76·7±2·0	73·0±2·1
% ARFC	41·6±2·2	44·0±3·9	46·2±2·2
TRFC/mm^3	1911±145	1448±206	1833±352
ARFC/mm^3	904±104	847±175	1147±218

* $P < 0{\cdot}05$ compared with %TRFC for stage II patients.

patients with fibroadenomas ($P < 0{\cdot}01$). However, all other differences among the groups of patients with benign mastopathy were not significant.

Differentiation between operable breast carcinoma and benign mastopathy

The rate of positive assay results was highest in patients with the best prognosis by stage (93·5 per cent in stage I). BTA-sensitive T cell detection by the AgARFC assay was positive in 85·1 per cent of patients with resectable breast carcinoma (stages I and II, combined). This overall incidence of positive BTA-sensitive T cell assays in patients with stages I and II breast carcinoma was significantly higher than in any of the benign mastopathy groups ($P < 0{\cdot}025$ to $P \ll 0{\cdot}0005$, *Table V*).

Peripheral lymphocyte counts and non-specific T cell subpopulations in patients with breast carcinoma

The mean values of peripheral blood lymphocyte counts, percentage or absolute number of circulating total T cells (TRFC) and percentage or absolute number of active T cells (ARFC), were not highly significantly different among stage I, stage II and stages III–IV breast carcinoma patients (*Table VI*).

Discussion

Positive responses to soluble breast tumour associated antigens by circulating T lymphocytes were detected in 93·5 per cent of patients with early invasive breast carcinoma by the antigen-stimulated active rosette-forming T cell (AgARFC) assay. Significantly lower percentages of patients with axillary nodal metastases, locally advanced disease and widespread breast cancer were positive. The relationship between pathological tumour stage and incidence of circulating BTA-sensitive T cells confirms previous findings reported from this laboratory (Ramey et al., 1979a, b). Furthermore, the relationship of decreasing cell mediated immune responses to BTA with advancing tumour stage shown in this study is in agreement with other reports which demonstrated depressed cell mediated immunity in advanced breast cancer. Disease stage and patient survival have been correlated with depressed delayed hypersensitivity reactions to autologous tumour transplants (Southam et al., 1962; Brunschwig et al., 1965) and to cryostat sections of autologous tumour tissue applied to skin windows (Black and Leis, 1971); however, the relationship of disease stage to skin test responses to soluble breast carcinoma tissue extracts has not been clearly defined (Hughes and Lytton, 1964; Stewart and Orizaga, 1971). Leucocyte migration inhibition (LMI) induced by BTA antigens has been shown to correlate with clinical stage and prognosis in several studies (Black et al., 1975; Roberts and Bathgate, 1975; Rieche et al., 1976). The highest degree of LMI reactivity to autologous and allogeneic breast tumour antigen was demonstrated in patients with *in situ* and early invasive breast carcinoma. Leucocyte adherence inhibition (LAI) induced by breast carcinoma antigen extracts was reported to be most frequent with leucocytes from patients with stage I or II breast carcinoma, while progressively lower rates of LAI reactivity were assayed with patients with stage III (45 per cent), or stage IV (29 per cent) disease (Grosser and Thompson, 1975; Fujisawa et al., 1977; Sanner et al., 1979). These results are in agreement with the incidence of BTA-sensitive T cells detected by the AgARFC assay in different pathological stages of breast cancer.

The mechanism underlying the unresponsiveness of T lymphocytes from patients with advanced breast cancer to BTA in the AgARFC assay has not been established. General parameters of cellular immune competence measured in this study were not significantly depressed in patients with stages II, III or IV breast cancer. In other studies, lymphoproliferative (LP) responses to alloantigens were depressed in patients with breast cancer, even when LP responses to mitogens were normal (Golub et al., 1974; Dean et al., 1977; Jerrells et al., 1978a, b). Mitogen-responsive T lymphocytes were correlated with the ARFC subpopulation whereas alloantigen-responsive T cells were correlated with the non-ARFC T cell subpopulation (Jerrells et al., 1978a). Similarly, BTA-sensitive T cells were detected in the non-ARFC subpopulation by the AgARFC assay, as were alloantigen-sensitized T cells in allotransplantation studies (Ramey et al., 1977; Burrows et al., 1978). Depressed LP reactivity of circulating alloantigen-sensitive T cells and depressed AgARFC reactivity of circulating BTA-sensitive T cells in patients with breast carcinoma may be the result of either depletion of such cells from the circulating lymphocyte pool, or excess of the sensitizing antigen which has been shown to block lymphocyte responses in the AgARFC assay (Hashim et al., 1979). Breast cancer serum has been shown to exert blocking activity on circulating leucocytes in a number of *in vitro* assay systems (Vanky et al., 1971; Whitehead et al., 1976; Jeejeebhoy, 1977; Steward, 1977), attributed to either antigen-antibody complexes (Sjogren et al., 1971; Matthews and Whitehead, 1976; Hoffken et al., 1977; Nordquist et al., 1977), or to excess circulating free tumour antigen (Grosser and Thomson, 1976; Fujisawa et al., 1977; Steward, 1977). Depression of BTA-sensitive T cells observed with AgARFC assays of peripheral blood lymphocytes of patients with advanced breast cancer could, therefore, represent an *in vivo* effect of either excess tumour antigen, or of tumour antigen-antibody complexes.

Recognition of breast tumour associated antigens by circulating T cells was observed in 23·0 per cent of patients with benign mastopathy. These responses may reflect the development of immunity to early malignant change in a continuum of breast disease progressing from benign mastopathy through 'pre-cancerous' hyperplastic lesions to *in situ* and eventually invasive carcinoma (Kern and Brooks, 1969; Black, 1976; Black et al., 1976; Cardiff et al., 1977). Recognition of BTA by patients with benign mastopathy has been reported in serologic assays (Humphrey et al., 1974), and LAI assays (Sanner et al., 1979) to a similar degree to that observed in the AgARFC assay. Higher rates of response in benign mastopathy have been reported with LMI (Cannon et al., 1978) and cell mediated cytotoxicity (Fossati et al., 1972; Avis et al., 1974; Oldham et al., 1975; Avis et al., 1976; Canevari et al., 1976) assays.

The incidence of BTA-sensitive T cells detected was significantly higher in patients with fibrocystic disease than in patients with fibroadenomas. This 3·6-fold increase in the incidence of positive assays for BTA-sensitive T cells in fibrocystic disease over the incidence with fibroadenomas parallels the increased risk of eventual breast cancer development associated with fibrocystic disease (Warren, 1940; Haagensen, 1956; Davis et al., 1964; Veronesi and Pizzocara, 1968). The question of whether these patients with fibrocystic disease will eventually develop invasive breast carcinoma was not addressed in this study; however, the data suggest that the AgARFC assay may be detecting early malignant change in fibrocystic disease. Such reactivity may have been responsible for the BTA-sensitive T cells noted in 5 of 10 patients with benign lesions consisting of perivascular or periductular lymphocyte infiltrates. Alternatively, these cases may represent reactivity to an agent similar to the murine mammary tumour viruses, which are known to cross-react with human benign and malignant proliferative breast lesions (Black et al., 1975; Muller et al., 1976).

The diagnostic accuracy of the AgARFC assay in the detection of resectable breast cancer by the criteria employed in this study was 95·3 per cent for stage I lesions and was 85·1 per cent for stages I and II combined. These percentages compare favourably with those reported for other *in vitro* assays, as well as with the detection rates which have been reported with mammography (Feig et al., 1977). Circulating T lymphocyte sensitization to breast tumour associated antigen was observed with significantly lower frequency in patients with advanced mammary carcinoma, non-mammary carcinoma or benign mastopathy. The incidence of BTA-sensitive T cells detected in patients with fibrocystic disease was higher than that in patients with fibroadenomas, by a factor which is in agreement with the increased breast cancer risk rate associated with fibrocystic disease. The data from this study suggest that the AgARFC assay reliably detected early invasive breast carcinoma, at the stage when it carries the most favourable prognosis. Longitudinal study of the patients assayed by the AgARFC method will assess the relevance of the detection of T cell sensitization to breast tumour associated antigens in determining prognosis of patients with breast carcinoma, and evaluate the possibility that detection of BTA-sensitive T cells in patients with fibrocystic disease reflects early malignant transformation.

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References

AMERICAN JOINT COMMITTEE FOR CANCER STAGING AND END-RESULTS REPORTING (1977) *Manual for Cancer Staging*. Chicago, Ill., pp. 101–107.

AVIS F., AVIS I., NEWSOME J. F. et al. (1976) Antigenic cross-reactivity between adenocarcinoma of the breast and fibrocystic disease of the breast. *J. Natl Cancer Inst.* **56**, 17–25.

AVIS F., MOSONOV I. and HAUGHTON G. (1974) Antigenic cross-reactivity between benign and malignant neoplasms of the human breast. *J. Natl Cancer Inst.* **52**, 1041–1049.

BLACK M. M. (1976) Structural antigenic and biological characteristics of precancerous mastopathy. *Cancer Res.* **36**, 2596–2604.

BLACK M. M. and LEIS H. P. JUN. (1971) Cellular responses to autologous breast cancer tissue. *Cancer* **28**, 263–273.

BLACK M. M., ZACHRAN R. E., SHORE B. et al. (1975) Prognostically favorable immunogens of human breast cancer tissue: antigenic similarity to murine mammary tumor virus. *Cancer* **35**, 121–128.

BLACK M. M., ZACHRAN R. E., SHORE B. et al. (1976) Biological considerations of tumor-specific and virus-associated antigens of human breast cancers. *Cancer Res.* **36**, 769–774.

BRUNSCHWIG A., SOUTHAM C. M. and LEVIN A. G. (1965) Host resistance to cancer: clinical experiments by homotransplants, autotransplants and admixture of autologous leukocytes. *Ann. Surg.* **162**, 416–425.

BURROWS W. B., PIERCE J. C., HASHIM G. A. et al. (1978) Cell mediated immunity to donor antigens in renal allograft recipients. *Surgery* **83**, 741–745.

CANEVARI S., FOSSATI G. and DELLA PORTA G. (1976) Cellular immune reaction to human malignant melanoma and breast carcinoma cells. *J. Natl Cancer Inst.* **56**, 705–709.

CANNON G. B., MCCOY J. L., JEROME L. J. et al. (1978) Immunologic relationship between breast carcinoma and benign breast disease as detected by the leukocyte migration inhibition assay. *J. Natl Cancer Inst.* **61**, 1181–1186.

CARDIFF R. D., WELLINGS S. R. and FAULKIN L. J. (1977) Biology of breast preneoplasia. *Cancer* **39**, 2734–2736.

DAVIS H. H., SIMONS M. and DAVIS J. B. (1964) Cystic disease of the breast: relationship to carcinoma. *Cancer* **17**, 957–978.

Dean J. H., Connor R., Herberman R. B. et al. (1977) The relative proliferation index as a more sensitive parameter for evaluating lymphoproliferative responses of cancer patients to mitogens and alloantigens. *Int. J. Cancer* **20**, 359–370.

Farrow J. H. (1970) Current concepts in the detection and treatment of the earliest of breast cancers. *Cancer* **25**, 468–477.

Feig S. A., Shaber G. S., Schwartz G. F. et al. (1977) Thermography, mammography and clinical examination in breast cancer screening. Review of 16 000 studies. *Radiology* **122**, 123–127.

Fossati G., Canevari S., Della Porta G. et al. (1972) Cellular immunity to human breast carcinoma. *Int. J. Cancer* **10**, 391–396.

Fujisawa T., Waldman S. R. and Yonemoto R. H. (1977) Leukocyte adherence inhibition by soluble tumor antigens in breast cancer patients. *Cancer* **39**, 506–513.

Golub S. H., O'Connell T. X. and Morton D. L. (1974) Correlation of *in vivo* and *in vitro* assays of immunocompetence in cancer patients. *Cancer Res.* **34**, 1833–1837.

Grosser N. and Thomson D. M. (1975) Cell mediated immunity in breast cancer patients evaluated by antigen-induced leukocyte adherence inhibition in test tubes. *Cancer Res.* **35**, 2571–2579.

Grosser N. and Thomson D. M. (1976) Tube leukocyte (monocyte) adherence inhibition assay for the detection of antitumor immunity. II. Monocyte reacts with tumor antigen via cytophilic antitumor antibody. *Int. J. Cancer* **18**, 48–57.

Haagensen C. D. (1956) *Diseases of the Breast*. Philadelphia, Saunders, pp. 156–66.

Harris J. E. and Sinkovics J. G. (1976) *The Immunology of Malignant Disease*. St Louis, Mosby, pp. 48–51, 55, 480–4.

Hashim G. A., Lee D. and Pierce J. C. (1977) Antigen stimulated rosette formation by sensitized T cells in experimental allergic encephalomyelitis. *Neurochem. Res.* **2**, 99–109.

Hashim G. A., Lee D., Pierce J. C. et al. (1978) Myelin basic protein stimulated rosette-forming T cells in multiple sclerosis. *Neurochem. Res.* **3**, 37–48.

Hashim G. A., Yee N. and Ramey W. G. (1979) The kinetics of T-lymphocyte subpopulations in guinea-pigs sensitized with allogeneic transplantation antigens. (Submitted for publication.)

Herberman R. H. (1976) Immunologic approaches to the diagnosis of cancer. *Cancer* **37**, 549–562.

Hoffken K., Meredith I. D., Robins R. W. et al. (1977) Circulating immune complexes in patients with breast cancer. *Br. Med. J.* **2**, 218–220.

Hughes L. E. and Lytton B. (1964) Antigenic properties of human tumours: delayed cutaneous hypersensitivity reactions. *Br. Med. J.* **1**, 209–212.

Humphrey L. J., Estes N. C., Muse P. A. Jun. et al. (1974) Serum antibody in patients with mammary disease. *Cancer* **34**, 1516–1520.

Jeejeebhoy H. F. (1977) Comparison of autochthonous and allogeneic breast tumour cells in tests for lymphocyte immunity to human tumours. *Br. J. Cancer* **35**, 161–169.

Jerrells T. R., Dean J. H. and Herberman R. B. (1978a) Relationship between T lymphocyte levels and lymphoproliferative responses to mitogens and alloantigens in lung and breast cancer patients. *Int. J. Cancer* **21**, 282–290.

Jerrells T. R., Dean J. H., Richardson G. L. et al. (1978b) Role of suppressor cells in depression of *in vitro* lymphoproliferative responses of lung cancer and breast cancer. *J. Natl Cancer Inst.* **61**, 1001–1009.

Kern W. H. and Brooks R. N. (1969) Atypical epithelial hyperplasia associated with breast cancer and fibrocystic disease. *Cancer* **24**, 668–675.

Matthews N. and Whitehead R. H. (1976) Inhibition of K cell function by human breast cancer sera. *Br. J. Cancer* **34**, 635–640.

Muller M., Zotter S. and Kemmer C. (1976) Specificity of human antibodies to intracytoplasmic type A particles of the murine mammary tumor virus. *J. Natl Cancer Inst.* **56**, 295–303.

Nordquist R. E., Anglin J. H. and Lerner M. P. (1977) Antibody induced antigen redistribution and shedding from human breast cancer cells. *Science* **197**, 366–367.

Oldham R. K., Djeu J. Y., Cannon G. B. et al. (1975) Cellular microcytotoxicity in human tumor systems: analysis of results. *J. Natl Cancer Inst.* **55**, 1305–1318.

Order S. E. (1977) Antigens, immunoglobulins and immunity during the course of breast cancer. *Prog. Clin. Biol. Res.* **12**, 119–130.

Ramey W. G., Hashim G. A., Burrows W. B. et al. (1979a) Cell-mediated immunity to breast cancer: tumor antigen sensitive circulating T-lymphocytes. *Fed. Proc.* **38**, 993.

Ramey W. G., Hashim G. A., Burrows W. B. et al. (1979b) Detection of breast tumour-antigen-sensitive circulatory T lymphocytes by antigen-stimulated active rosette formation.*Cancer Res.* **39** (In the press.)

Ramey W. G., Hashim G. A., Pierce J. G. et al. (1977) A new assay for T cell mediated immunity to transplantation antigens. *Surgery* **81**, 640–645.

Reisfeld R. A. and Kahan B. D. (1970) Transplantation antigens. *Adv. Immunol.* **12**, 117–200.

Rieche K., Arndt A. and Pasternak G. (1976) Cellular immunity in mammary cancer patients as measured by the leukocyte migration test. A follow up study. *Int. J. Cancer* **17**, 212–287.

Roberts M. M. and Bathgate E. M. (1975) The immune reaction to human breast cancer: a comparison of skin and leucocyte migration tests. *Br. J. Surg.* **62**, 870–872.

Sanner T., Brennhovd I., Christensen I. et al. (1979) Cellular antitumor immune response in women with risk factors for breast cancer. *Cancer Res.* **39**, 654–657.

Sjogren H. O., Hellstrom I., Bausal S. C. et al. (1971) Suggestive evidence that the 'blocking' antibodies of tumor-bearing individuals may be antigen-antibody complexes. *Proc. Natl Acad. Sci.* **68**, 1372–1375.

Southam C. M., Brunschwig A. and Dizon Q. (1962) Autologous and homologous transplantation of human cancer. In: *Henry Ford Hospital International Symposium: Biological Interactions in Normal and Neoplastic Growth*. Boston, Little, Brown.

Steward A. M. (1977) The modulation of tumour versus host response in lung, colon and breast cancer patients: implications for adjuvant immunochemotherapy. *Aust. NZ J. Surg.* **47**, 642–647.

Stewart T. H. M. and Orizaga M. (1971) The presence of delayed hypersensitivity toward cellular extracts of malignant tumors. The frequency and cross-reactivity of this phenomenon in breast cancer and its correlation with survival. *Cancer* **28**, 1472–1478.

Vanky F., Stjensward J., Klein G. et al. (1971) Serum-mediated inhibition of lymphocyte stimulation by autochthonous human tumors. *J. Natl Cancer Inst.* **47**, 95–103.

Veronesi U. and Pizzocara G. (1968) Breast cancer in women subsequent to cystic disease of the breast. *Surg. Gynecol. Obstet.* **126**, 529–532.

Warren S. (1940) The relation of 'chronic mastitis' to carcinoma of the breast. *Surg. Gynecol. Obstet.* **71**, 257–273.

Waters H. (1978) *The Handbook of Cancer Immunology, Vol. 1: Basic Cancer-related Immunology*. New York, Garland STPM Press.

Whitehead R. H., Thatcher J. and Teasdale C. (1976) T and B lymphocytes in breast cancer: stage relationship and abrogation of T lymphocytes depression by enzyme treatment *in vitro*. *Lancet* **1**, 330–333.

Zimmerman A., Ruchti C., Roos B. et al. (1977) The problem of immunity to breast cancers. *Prog. Clin. Biol. Res.* **12**, 75–89.

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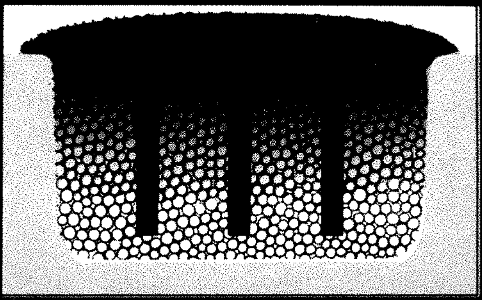

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The distribution, size and density of the apocrine glands in hidradenitis suppuritiva

W. P. MORGAN AND L. E. HUGHES*

SUMMARY

The distribution, size and density of the apocrine glands in hidradenitis suppuritiva as compared with those in axillary hyperhidrosis and normal controls have been studied. There are no significant differences in the size or density of the apocrine glands in hidradenitis suppuritiva as compared with normal controls. The apocrine glands in axillary hyperhidrosis are significantly larger than those in axillary hidradenitis and in normal controls.

A simple method that can be used to demonstrate the distribution of the apocrine glands preoperatively is described. This has proved useful in delineating the area which it is necessary to excise to obtain complete apocrine gland excision in the diseased area. The apocrine gland-containing skin in the diseased region does not always correspond exactly to the hair-bearing area in that region.

HIDRADENITIS suppuritiva is a chronic, cicatrizing, suppurative disease of skin and subcutaneous tissue first described by Velpeau in 1839. The condition occurs in both males and females, though most series show a female predominance. It commences after puberty, most commonly in the second or third decade, and is usually considered to be a disorder of the apocrine glands as it is largely localized to areas where apocrine glands are found.

Treatment for this condition is unsatisfactory. Medical treatment is largely ineffective and seeks to palliate the established condition. Surgery cannot be considered entirely satisfactory since conservative resections are followed frequently by recurrence, and radical excisions are painful and result in a long period of morbidity before healing is complete. The unsatisfactory nature of current therapy may reflect the paucity of knowledge of these glands.

The apocrine sweat glands are simple, coiled, tubular glands with shunts and diverticula which lie mainly in the dermis, but large glands, as in the axilla, may extend into the subcutaneous fat, as much as 5 mm below the skin surface (Montagna and Parakkal, 1974). Apocrine sweating is adrenergically controlled but there is doubt as to the exact mechanism by which the catecholamines reach the glands. Hurley and Shelley (1960) suggest that apocrine sweating is divided into two phases. The first phase consists of secretion of sweat into the apocrine tubule and the second of expulsion of the apocrine sweat from the gland on to the skin surface. It is thought that the stimuli of apocrine sweating act by causing contraction of the myoepithelial cells surrounding the apocrine tubule, propelling sweat up the duct on to the skin surface. This rather meagre knowledge of the apocrine glands is largely confined to normal patients. There is little evidence to indicate whether apocrine glands differ quantitatively or qualitatively from normal in patients who develop hidradenitis.

Hidradenitis arises wherever apocrine sweat glands are situated. These are seen mainly in the axillae (where they are most dense), the external genitalia, the pubo-inguino-perineal and perianal regions. Certain modified apocrine glands also develop; the ceruminous glands of the external auditory meatus, the glands of Moll in the eyelids and the breast. The hair follicles in other regions usually fail to develop apocrine glands. However, the continued development of apocrine primordia in regions such as the scalp, the beard region and the trunk after the fifth month of intrauterine life results in heterotopic apocrine glands.

While the distribution of apocrine glands has been mapped in the general terms outlined here, no studies have been reported which define their distribution in exact terms, such as would be required to describe an operation for complete excision of the apocrine glands.

These deficiencies in the knowledge of the apocrine glands have led us to study two aspects of the background to hidradenitis suppuritiva. First, we have attempted to determine whether apocrine glands differ in number or size in patients with hidradenitis suppuritiva when compared with controls. Patients with hyperhidrosis (excessive eccrine sweat secretion) have also been studied in this regard. Secondly, an attempt has been made to develop a technique for demonstrating the distribution of apocrine glands prior to operation. This is being used both to delineate the area of skin which it is necessary to excise to obtain apocrine gland excision in patients with hidradenitis, and in the longer term, to determine whether the distribution of these glands differs from that in normal subjects.

Frequency and size of apocrine glands in hidradenitis

Methods

Pieces of skin 1 cm square were excised from the apices of the axillae in patients undergoing surgery for hidradenitis or hyperhidrosis, and in normal patients of similar age and sex undergoing other operations in this area. Similarly, specimens were excised from the hair-bearing skin overlying the pubic tubercle in patients with hidradenitis and normal patients undergoing operations in this region.

Following fixation of the specimen, 5-μm vertical sections of the skin were cut every 1 mm, resulting in 10 sections per specimen. After staining with haematoxylin and eosin, the number of glands in the ten sections was counted. Density was expressed as glands/cm^2. The index of size was determined by measuring the diameters of the apocrine glands in each skin specimen. The greatest diameter of an apocrine gland per 10 sections was taken as the index of the size in that skin specimen, since variation in the 10 sections through the spherical glands would result in less than maximal diameter in many cases.

In some of the axillary specimens there was near confluence of the apocrine tubules. Division of the tubules into separate units of apocrine glands was determined by the width of connective tissue partitions between the glands and by the height of the tubular epithelium. While the height of the tubular epithelium may be columnar, cuboidal or squamous, in general the height of the cells lining the tubules of one apocrine gland tends to be constant.

The third parameter measured was the total surface area of apocrine tubules in the 10 sections. A modified form of

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Table I: AXILLARY RESULTS

Parameters measured	HH ($n = 6$)	HS ($n = 20$)	CTL ($n = 10$)
Glands/cm² (medians)	84	78	62
HH > CTL	U = 16·5 $P > 0·1$		
HS > CTL	U = 80 $P > 0·1$		
HH > HS	U = 59·5 $P > 0·1$		
Maximum apocrine diameter mm (medians)	2·835	2·5	2·35
HH > CTL	U = 1 $P < 0·001$		
HS > CTL	U = 69·5 $P > 0·1$		
HH > HS	U = 26 $P < 0·05$		
Surface area mm² (medians)	93·63	46·81	33·51
HH > CTL	U = 14 $P > 0·1$		
HS > CTL	U = 75 $P > 0·1$		
HH > HS	U = 28 $0·05 < P < 0·1$		
[Surface area mm²]/[glands/cm²]	1·0135	0·57915	0·49
HH > CTL	U = 10 $P < 0·05$		
HS > CTL	U = 75 $P > 0·1$		
HH > HS	U = 17 $P < 0·02$		

HH, Hyperhidrosis; HS, hidradenitis; CTL, control.
U = Mann–Whitney U test.

Table II: PERINEAL RESULTS

Parameters measured	HS ($n = 15$)	CTL ($n = 9$)
Glands/cm² (medians)	0 ($\frac{2}{3} = 0$) U = 65 $P > 0·1$	0 ($\frac{2}{3} = 0$)
Maximum apocrine diameter mm (medians)	1·0 U = 5·5 $P > 0·1$	0·6
Surface area mm² (medians)	0 ($\frac{2}{3} = 0$) U = 64 $P > 0·1$	0 ($\frac{2}{3} = 0$)

HS, Hidradenitis; CTL, control.
U = Mann–Whitney U test.

planimetry utilizing the Quantimet 70 (Cambridge Instruments Ltd) was used for this purpose. The section to be studied was placed under the microscope of this instrument, which transmitted the image of the section on to a television screen. The margins of the apocrine tubules were then marked out on the screen by a light pencil, from which the Quantimet 70 calculated the surface area of the apocrine tubules, expressed in mm².

Results

Specimens were obtained from the apex of the axilla in 36 patients, 20 with hidradenitis, 6 with hyperhidrosis and 10 normal controls. The results obtained for the three parameters of size, density and total surface area are shown in *Table I*. As the results did not show a normal distribution, the significance was analysed using the Mann–Whitney U test.

There is no significant difference between the number of glands/cm² in any of these three groups.

The maximum diameters of the apocrine glands in hidradenitis did not differ from those in normal controls. However, the apocrine glands in hyperhidrosis were consistently large, the maximum diameters being significantly increased when compared with those of hidradenitis patients and normal controls.

There was no significant difference in the total surface area of apocrine tubules in any of the three groups. The median surface area of the apocrine tubules in hyperhidrosis was increased as compared to hidradenitis, but the result was only of borderline significance. The ratio of total surface area to number of glands/cm² is probably the best index of the average size of the apocrine glands in each group. This ratio was significantly increased in hyperhidrosis as compared with hidradenitis and normal axillary controls.

Specimens of hair-bearing skin over the pubic tubercle were studied in 24 patients, 15 hidradenitis patients and 9 normal controls. The results are shown in *Table II*. Two-thirds of the samples shown in each group contained no apocrine glands. This resulted in medians of 0 for glands/cm² and surface area in each group. In those specimens that did contain apocrine glands, there was no significant difference in the maximum diameter of each group.

Preoperative mapping of apocrine glands in hidradenitis

Methods

Wada's (1950) iodine/starch method is widely used in determining the area of maximal secretion of eccrine sweat in hyperhidrosis, but it does not differentiate between apocrine and eccrine sweat. Both forms of sweat will give a black spot when they facilitate mixing of the iodine/starch. To overcome this, we have developed a method in which eccrine sweating is blocked with atropine, following which oxytocin is given to stimulate apocrine sweating by contraction of the myoepithelial cells about the apocrine tubule. This is then demonstrated by the iodine/starch method.

It is necessary to ascertain prior to the procedure that the patient is normotensive and is not pregnant. The skin of the region under study should be shaved 48 h before the procedure because firm stroking of the skin expresses apocrine sweat and apocrine glands have a refractory period of 24–48 h after stimulation (Hurley and Shelley, 1960). Atropine (1·2 mg) is administered intravenously. The skin is then cleansed with alcohol, followed by the application of 2 per cent iodine in alcohol solution to the area under study and to the palm of the hand. When dry, a mixture of 75 g fine starch powder in 100 ml castor oil is applied to the area under study and to the palm of the hand. Oxytocin (2 i.u.) is given slowly intravenously. Within 3–5 min the black spots of apocrine sweating can be seen around the base of regional hair and at extrafollicular sites. The palm of the hand is used as a control to ensure that eccrine sweating has been completely blocked by the atropine, since this skin contains numerous eccrine but no apocrine glands.

The area of apocrine gland distribution in the axilla or pubo-inguino-perineal region was mapped out prior to radical excision for hidradenitis and the distribution of glands was determined in the resected specimen in the following way.

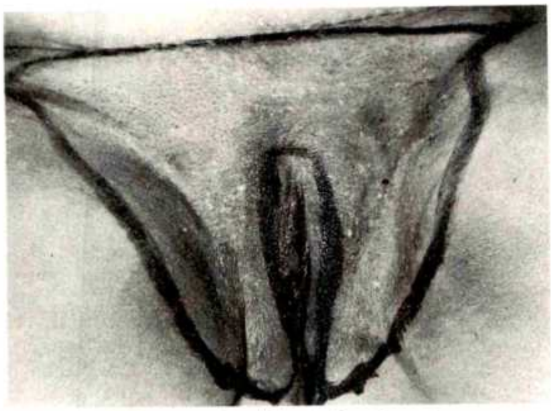

Fig. 1. Marked extent of excision in female perineum.

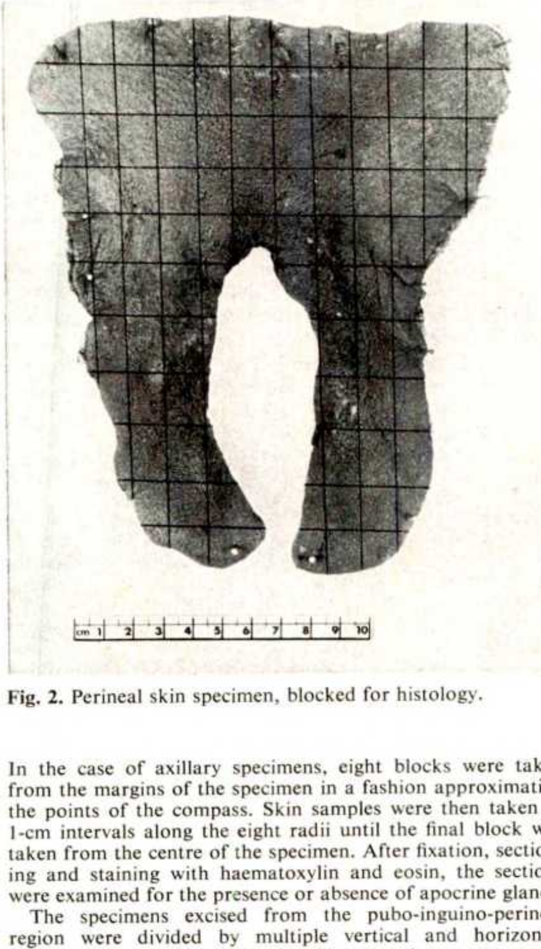

Fig. 2. Perineal skin specimen, blocked for histology.

In the case of axillary specimens, eight blocks were taken from the margins of the specimen in a fashion approximating the points of the compass. Skin samples were then taken at 1-cm intervals along the eight radii until the final block was taken from the centre of the specimen. After fixation, sectioning and staining with haematoxylin and eosin, the sections were examined for the presence or absence of apocrine glands.

The specimens excised from the pubo-inguino-perineal region were divided by multiple vertical and horizontal incisions into a grid of blocks. Three sections were cut at intervals from each block, and after staining the presence or absence of apocrine glands in the sections was noted (*Figs.* 1 and 2). In this way, a map of the apocrine glands in this region was drawn up.

Results

The atropine/iodine/starch and oxytocin method has been used to demonstrate the distribution of the apocrine glands in 11 axillary (6 male and 5 female) and 8 perineal (5 female and 3 male) regions. The sweat droplets appear as small black dots, mainly about the base of a hair, but also at extrafollicular sites. The spots are necessarily small, as the amount of sweat produced by one apocrine gland is 0·001 ml (Hurley and Shelley, 1960). In the axillae the apocrine glands are most dense in the skin of the hair-bearing area, but droplets in a less dense distribution may extend a further 2–3 cm outside this area (*Fig.* 3).

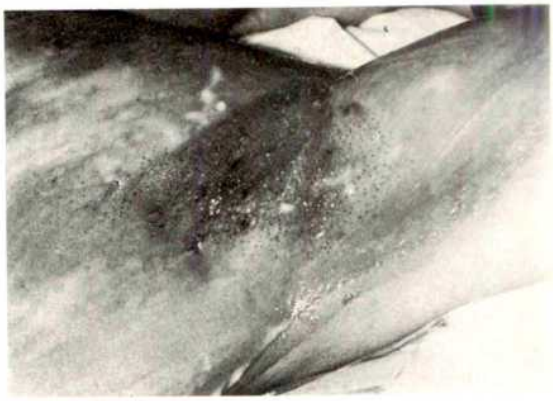

Fig. 3. Apocrine droplets in the axilla.

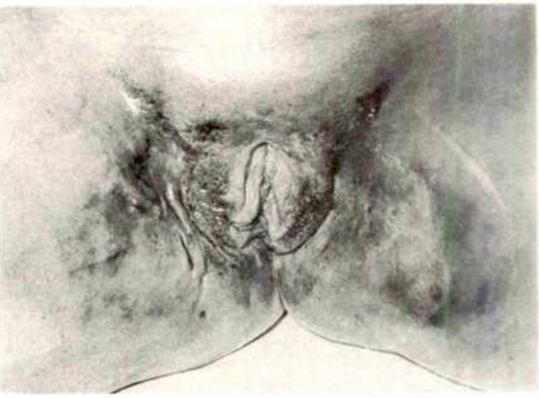

Fig. 4. The distribution of apocrine sweating in the female perineum.

In the perineum the majority of the apocrine glands, as demonstrated by the iodine/starch and oxytocin method, are situated in the skin of the medial halves of the flexural creases of the groins, extending posteriorly towards the anus. In the female they are present in the skin of the labia majora (*Fig.* 4) and in the male in the skin around the root of the penis and of the scrotum. Apocrine glands are also situated in the skin of the pubic region in a less dense fashion. The iodine/starch and oxytocin method also demonstrates the presence of variable thinly scattered heterotopic apocrine glands over the trunk.

Twenty-two axillary specimens (15 female and 7 male) and 9 perineal specimens (8 female and 1 male) were examined histologically. The maps of the apocrine glands so obtained confirmed the distribution of the apocrine glands in these regions, as demonstrated by the atropine/iodine/starch and oxytocin method. In the hair-bearing area of the axilla the glands can be near confluent, but in the surrounding

2–3 cm of skin apocrine glands can be found, often as solitary glands. In the perineum the glands were smaller and sparser than in the axilla.

Discussion

Shelley and Cahn (1955) produced keratinous plugging in the axillae of 12 normal male subjects by applying perforated belladonna adhesive tape to manually epilated axillary skin. At the end of 1 week all the subjects developed apocrine anhidrosis in these areas. Three of the 12 developed small, deep, tender nodules localized to the tape sites with the clinical appearance of hidradenitis suppuritiva. Histological study of the lesions showed keratinous plugging of the apocrine duct, dilatation of the apocrine duct and severe inflammatory changes limited to a single apocrine sweat gland.

Our work has not demonstrated any differences in the size or density of the apocrine glands in hidradenitis compared with those in controls. It is therefore possible that the primary pathology in hidradenitis suppuritiva is plugging of the apocrine ducts leading to an outlet obstruction of otherwise normal glands. Paradoxically, the size of the apocrine glands in axillary hyperhidrosis was significantly increased as compared with those in axillary hidradenitis and normal controls. A striking feature of the apocrine glands in hyperhidrosis was the uniformly large size of the glands in the samples examined. It is clear that the apocrine glands in hyperhidrosis are being subjected to some form of maximal stimulation, resulting in a full expression of their growth potential, but what form this stimulus takes is unknown. We are not aware of an association between hyperhidrosis and hidradenitis, and in fact the hyperactivity of the glands in hyperhidrosis might protect against hidradenitis, in that duct blockage seems to be the primary pathology.

The atropine/iodine/starch and oxytocin technique is a satisfactory method of demonstrating the distribution of the apocrine sweat glands. Its major practical use is to demonstrate the distribution of the apocrine sweat glands in a diseased region. Theoretically, it is then possible to achieve complete excision of all the apocrine gland-containing skin in that region and, hence, cure of the condition. Only a long term study can verify this. There are a number of possible limitations to the complete success of the method. While the major concentrations of the apocrine glands are well localized in both axillae and perineum, scattered apocrine glands are present over the trunk. It would not be possible in terms of morbidity and cosmesis to extend the excision to include these glands. In the male, the scrotal skin contains apocrine glands: while excision of diseased scrotal skin with a normal margin is acceptable to the patient, complete ablation of the scrotal skin is unlikely to be so. Recurrence of the condition could, then, occur either in the scattered trunk glands or in the scrotum. In the long term the technique can be used to compare the distribution of the apocrine glands in hidradenitis patients and normal controls.

Conclusions

Microscopic examination of skin samples obtained from the axillary and pubo-inguino-perineal regions did not show any significant difference in the size and density of the apocrine glands in cases of hidradenitis suppuritiva and normal controls. There was a significant increase in the size of the apocrine glands in axillary hyperhidrosis as compared with those in axillary hidradenitis suppuritiva and normal controls.

The iodine/starch and oxytocin method demonstrates the distribution of the apocrine glands in the axillary and pubo-inguino-perineal regions and this distribution has been confirmed histologically. It also demonstrates the presence of scattered apocrine glands over the trunk. The method demonstrates the difficulties of achieving complete apocrine gland excision in the diseased region. In both sexes there are scattered apocrine glands over the trunk, and in the male the skin of the scrotum contains numerous apocrine glands. Excision of these areas, if not diseased, would yield a high morbidity and probably be unacceptable to the patient. It would seem reasonable that the surgeon should excise the main concentrations of apocrine glands in the axilla or perineum, as demonstrated by the method, with all diseased skin, accepting that a small proportion of cases will recur because of scattered or scrotal apocrine glands.

Acknowledgements

We are indebted to Mrs Glenys Elliott for her technical assistance.

References

HURLEY H. J. and SHELLEY W. B. (1960) *The Human Apocrine Sweat Glands in Health and Disease.* Springfield, Ill., Thomas, pp. 28, 30, 42.

MONTAGNA W. and PARAKKAL P. F. (1974) *The Structure and Function of Skin*, 3rd ed. New York, Academic Press.

SHELLEY W. B. and CAHN M. M. (1955) The pathology of hidradenitis suppuritiva in man. *Arch. Dermatol.* **72**, 562–565.

VELPEAU A. (1839) In: *Dictionnaire de Médecin, un Répertoire Général des Sciences Médicales sous la Rapport. Théorique et Pratique*, 2nd ed. Bechet Jeune. vol. 2, p. 91; vol. 3, p. 304; vol. 19, p. 1.

WADA M. (1950) Sudorific action of adrenalin on the human sweat glands and determination of their excitability. *Science* **111**, 376–377.

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Continent anal ileostomy with mucosal proctectomy: a bloodless technique using a surgical ultrasonic aspirator in dogs

W. J. B. HODGSON, J. L. FINKELSTEIN, PHILLIPA WOODRIFFE AND A. H. AUFSES JUN*

SUMMARY

At present, mucosal proctectomy with ileo-anal anastomosis is a difficult, time-consuming operation involving much blood loss, often associated with impaired postoperative continence. A new operation has been devised in our department in which a surgical ultrasonic aspirator, the CUSA™ System (Cavitron Corporation) was used to fragment directly and strip bloodlessly mucosa from the rectal wall in 20 dogs as part of a simple ileo-anal sleeve anastomosis. All dogs were closely followed for up to 10 months. The only operative mortality occurred in the first dog where the upper rectum sloughed because the superior haemorrhoidal artery was divided. Preoperative weight was regained within the first 2 months. Initially stools were loose and frequent. Within 2 weeks the daily stool count was 5–6 with gradual thickening to semisolid consistency by 6 weeks. Finally 3–4 normal stools were passed daily. Postoperatively, all dogs remained continent.

In pilot studies in animal and clinical work, (Hodgson et al., 1979; Hodgson et al., 1980a, b) a promising new surgical instrument has undergone preliminary evaluation, first at the Bronx Veterans Administration Medical Center and currently at the Mount Sinai Hospital, New York. This instrument incorporates, for the first time, ultrasonic energy in the actual performance of general surgical procedures. The initial evaluation demonstrated the capability of the ultrasonic aspirator to strip mucosa directly from the submucosa in the dog bowel. Furthermore, it could be done with minimal bleeding.

The first work in this field appeared in 1947, when Ravitch and Sabiston (1947) introduced the anal ileostomy with preservation of the anal sphincter in dogs. However, although it has since been used in patients, this procedure has not gained universal acceptance because it takes 2–3 hours of very careful dissection to perform the mucosal proctectomy (Martin et al., 1977). It was thought that the surgical ultrasonic aspirator might considerably reduce this time because of its ability to selectively fragment and aspirate tissue with a high water content and yet leave fibrous tissue relatively untouched. A study was therefore carried out in 20 dogs in which total colectomy was performed, leaving behind the rectum. Mucosal proctectomy was then carried out using the ultrasonic device which, on direct contact with the rectal mucosa, fragmented and aspirated it in its entirety. The endorectal pullthrough which followed was then done in the normal manner and the dogs observed for varying periods of time so that possible complications could be detected.

Materials and methods

The ultrasonic instrument

In 1969 the Kelman–Cavitron Phaco-Emulsifier™ was introduced for use in cataract surgery (Kelman, 1969). Subsequently results in over 500 cases have not demonstrated any particular problems which could be attributed solely to the Phaco-Emulsifier and the small percentage of cases which did develop problems was equivalent to the expected complication rate using other techniques (Kelman, 1973). Since then the Phaco-Emulsifier has become the preferred instrument in many centres (Jaffe, 1978). The Cavitron Ultrasonic Surgical Aspirator (CUSA™ System) is essentially a larger and more powerful version of the Phaco-Emulsifier and was first manufactured in February 1976. Initially it was intended to be used in neurosurgery and since Flamm et al. published their landmark paper in 1978, it is being used more and more frequently in this discipline.

The ultrasonic instrument basically consists of a control and power console operating with standard operating theatre electrical connections and to which is connected a gas-sterilizable handpiece. In general surgery a pencil grip surgical handpiece is used. It contains a vibrating suction device of hollow titanium oscillating longitudinally along its axis. This oscillation or vibration is produced by a magneto-strictive device which employs the principle of resonant vibration of a long slender metal structure. An alternating electric current, of exactly the frequency required to produce the mechanical vibration, is supplied by an electric oscillator in the console, and passes through the coil around the magneto-strictive transducers. When the alternating current is on, the transducer contracts and when the current is reversed, expansion of the transducer occurs beyond the original resting position. However, this contraction and expansion is not uniform but is very similar to the oscillations of a coiled spring attached to a weight. The tip contracts and expands simultaneously with the transducer. Because the hollow titanium tip is cone-shaped, this has the effect of amplifying the vibrations of the transducer and the resultant excursion of the tip, if plotted, would describe a sine wave. This is quite unlike low frequency reciprocating devices which vibrate uniformly and are limited, compared with the acoustic vibrators, in the velocities which may be obtained at their extremities.

The CUSA™ System operates at the ultrasonic frequency of 23 kHz. The vibration at the tip is imperceptible and has a maximum excursion of 150 μm and a total stroke of 300 μm. This vibration fragments tissue on contact and these tissue fragments are suspended in a stream of sterile normal saline flowing from the outside to the inside of the tip and removed from the operative field. This stream of normal saline is used at a rate of about 3–10 ml/min and can be varied as the operator desires. The ultrasonic vibration produces heat within the handpiece and at the tip. Reducing sterile irrigation increases the heat available at the tip so that a degree of cautery may be obtained. The magneto-strictive device is housed in a hollow stainless steel jacket and cooled by a stream of clean, but not sterilized, water drawn through the vacuum. If a defective seal or a crack in the housing occurred, the vacuum would prevent contamination of the handpiece. A plastic flue shrouds all but the last few millimetres of the tip and only this portion of the instrument is allowed contact with target tissue.

Maximal power available in the handpiece is approximately 75 W and depending on the requirements at the time of surgery

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this level can be varied at the console. The console has an onboard computer logic system which directs and monitors the procedure and assures that the unit is properly primed and that vibration and irrigation is set and checked. On/off switches for the ultrasonic power and for irrigation are provided on a footpiece. The console will shut off ultrasonic power automatically if the control is disabled for any reason. Maximal aspiration is 24 mmHg and this can be reduced at the console. Aspiration automatically becomes inoperative when applying flush irrigation and is momentarily interrupted whenever tip vibration is interrupted. If the tip should become overloaded for any reason the console will automatically shut off power. Operation at present requires a surgeon and a technician. The technician sets up and primes the control and power console and is handed the end of the sterile tubing containing the handpiece. This tubing is plugged into the console and the surgeon then commences the procedure. At the end of the procedure the tubing is discarded and a new CUSA™ PAK is provided for the next operation as it is impossible to clean out tubing adequately between cases.

The experiment

Twenty dogs weighing between 15 and 25 kg were used. Haemoglobin, haematocrit values and white blood counts were obtained in all dogs before and after surgery. Antibiotics were routinely given preoperatively and postoperatively for 5 days.

Fluids ad libitum were provided but food was stopped 24 h preoperatively. Bisacodyl enemas were given the morning and evening before surgery and also on the morning of the operation. Anaesthesia was induced using intravenous Nembutal after which the dog was intubated. The skin was prepared and shaved and the abdomen opened in a standard manner. The vessels and mesentery of the colon were divided and the terminal ileum mobilized, dividing arcuate vessels and mesentery as necessary but taking care to keep the marginal vessels intact, until the ileum could be brought down to the perineum. Care was also taken, except in the first dog, to ensure that the superior haemorrhoidal artery was not divided. The colon was removed after placing stay sutures in the walls of the rectum. The ultrasonic instrument was used to divide the colon at the rectosigmoid junction.

Babcock clamps were applied to the stump of the rectum and, at about three-quarters of full power, the ultrasonic tip was applied to the mucosa of the rectum which was aspirated from the submucosa. Initially this could be done visually but after all the mucosa from the top 2 cm of rectal stump had been removed, the tip had to be operated blind. Subsequently, therefore, the tip was used to ream out mucosa from the rectal wall. Progress was determined from time to time by palpation and the operation was continued as far as possible from above. When it was clear that the distance was too great to continue to ream out mucosa, the ultrasonic instrument was moved to the anus and passed through the anus to complete the mucosal stripping. At this point the terminal ileum was tied off with a double umbilical tape in order not to soil the denuded rectum. After being pulled through the anus, it was partially opened and sutures placed between it and the skin of the anus. The redundant ileum was removed and four stitches were usually adequate to complete the anastomosis. After copious irrigation of the peritoneal cavity, the abdomen was closed in a standard manner and the dogs were maintained on intravenous fluids overnight.

After 24 h fluids were offered to the dog and usually within 48 h soft food could be provided. The dog would normally be eating a standard diet within 1 week.

Results

As experience was gained the time of the operation was reduced to below 2 h and in particular the mucosal proctectomy could be carried out in 15 min. Very little bleeding occurred and haemoglobin and haematocrit values remained the same postoperatively as they were preoperatively. No infections secondary to surgery occurred. All dogs were continent of faeces throughout the experiment. When the stool was liquid, it was evacuated in the normal manner. Some post-evacuation anal soiling occurred with these liquid stools. No nocturnal incontinence occurred.

A set pattern developed in that the stool consistency gradually improved from diarrhoeal to semisolid during the first month. The frequency of bowel movements increased from once to six times daily during this month, declined to four times daily at 4 months and to between two and three times daily thereafter. The semisolid stool became of normal consistency by 5 months although one dog was producing normal stool at 3 months.

Maximum weight loss occurred at 6 weeks and was more pronounced in the smaller dogs (*Fig.* 1). Overall, the weight loss was 2–3 kg but weight was regained in 4–5 months. The larger dogs regained weight sooner.

Maximum follow-up time was 10 months (*Fig.* 2). Dogs were sacrificed at intervals and abdomino-perineal resection performed to determine the state of the ileoproctostomy. The first dog died at 10 days postoperatively and was found to have sloughed its upper rectum. In this dog the superior haemorrhoidal artery had been taken because this vessel is removed during anterior resection in the human without problems. Clearly, in the dog, this prejudiced the outcome and thereafter the superior haemorrhoidal was carefully preserved. Initially, the anastomosis was done in two layers. First the ileum was sutured with 3/0 chromic catgut from serosa to the raw surface of the rectum. Then 3/0 catgut was used to suture the open end of the ileum to the anal skin. This double closure was abandoned when dog number 13 developed a fistula in the terminal ileum which led to faecal soiling for the first 2 weeks. The intraperitoneal portion of the rectum was not routinely sutured to the ileum. None the less, firm adherence occurred between the proximal rectum and ileum within 2 weeks. However, distally, the terminal ileum retracted up to a maximum of 2 cm from the anus. Sometimes this retraction occurred as early as 2 weeks postoperatively. None the less the result after mucosal regrowth was very satisfactory with the terminal ileum looking rather like the cervix uteri and the rectum like the vaginal vault (*Fig.* 3). Using 3/0 nylon to perform the distal anastomosis diminished retraction somewhat but the natural tendency for the terminal portion to narrow continued. This problem was finally solved by performing multiple punctures in the terminal ileum through the serosa and muscle, down to submucosa, with the ultrasonic aspirator. The anastomosis was then done with a single layer of four sutures of 3/0 vicryl and retraction and narrowing was virtually eliminated.

Discussion

In order to guarantee extirpation of unstable colonic mucosa, patients with precancerous colonic conditions such as familial polyposis or Gardner's syndrome have had to submit to total proctocolectomy and ileostomy and, furthermore, patients with ulcerative colitis who do not respond to medical treatment have also had to submit to such radical procedures. Unfortunately surgery is frequently deferred unnecessarily because of the unwillingness of the patient to take the step of total proctocolectomy and ileostomy. This unwillingness to accept surgery is based on the very real embarrassment which may occur to the ileostomate

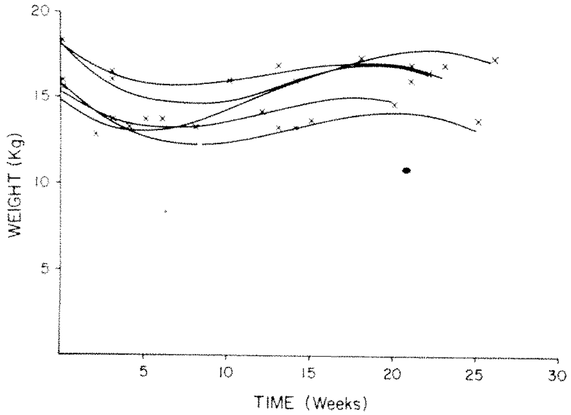

Fig. 1. Weight loss in dogs after colectomy and mucosal proctectomy with the ultrasonic aspirator.

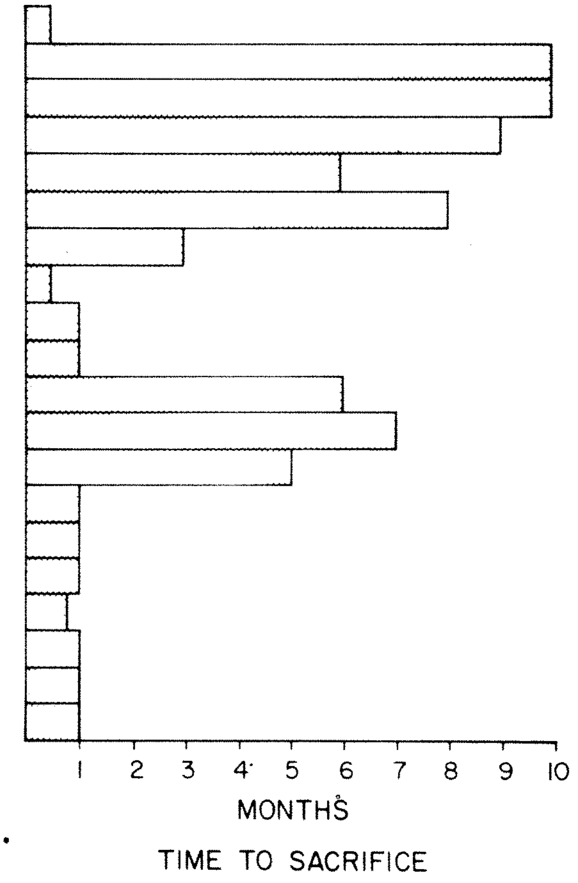

Fig. 2. Follow-up graph for dogs after colectomy and mucosal proctectomy with ultrasonic aspirator.

in courtship and marriage (Burnham et al., 1977), and to which must be added difficulties in sports and other strenuous activities. The presence of an ileostomy also precludes employment in the food industry. A Kock ileostomy has considerably assuaged these problems (Kock, 1969) but has not entirely eliminated them.

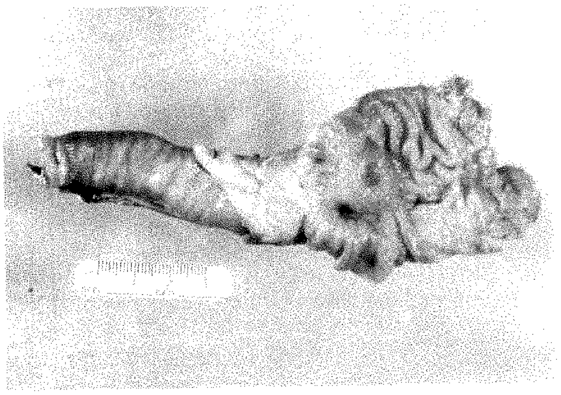

Fig. 3. Photograph of mucosal proctectomy and endorectal pullthrough 1 month after surgery.

The ideal operation for benign disease with potential malignancy would remove all potentially malignant mucosa and yet still preserve the anal sphincter. This not only avoids ileostomy, it also avoids the potential hazards of major pelvic dissections including possible damage to the nervi erigentes perhaps with poor bladder emptying and impotence in the male. A method of stripping the entire extraperitoneal rectal mucosa with minimum trauma, coupled with total abdominal colectomy and ileo-anal anastomosis, would best satisfy these criteria of an ideal operation. In addition, it would eliminate the lifelong attention necessary for the retained rectal segment and, of course, would obviate a permanent ileostomy for a benign disease. Ravitch and Sabiston (1947) and Ravitch and Handelsman (1951) successfully performed rectal mucosal proctectomy in dogs in 1947 and 1951; they described 7 patients with familial polyposis and ulcerative colitis who had undergone total colectomy and anal ileostomy. However, the operation, which was done from below and was quite traumatic, did not gain acceptance. In 1964 Soave modified the operation, performing it from above for the management of infants with Hirschsprung's disease. A similar technique was used by Jeffery, Hawley and Parks, who in 1976 reported a series of 5 patients who had a colo-anal sleeve anastomosis for diffuse cavernous haemangioma involving the rectum. However, the greatest experience of mucosal proctectomy and ileo-anal anastomosis was reported by Martin, LeCoultre and Shubert in 1977 who performed the procedure on 17 patients with ulcerative colitis. They found, even with the protection of the mucosal proctectomy with a temporary Turnbull loop ileostomy, that they had occasional postoperative problems due to haematoma formation and, in particular, once a temporary ileostomy was closed it took up to a year for complete control of the anal ileostomy to be obtained. Heiman et al. (1978) have been carrying out similar studies in patients with familial polyposis and in their admittedly small series of 4 cases have had no complications due to haematoma formation and have been able to manage the patients successfully after closure of the temporary ileostomy so that complete control of the anal ileostomy was obtained without medication within about 6 months.

These results would indicate that mucosal proctectomy and colo-anal or ileo-anal anastomosis should have a wider acceptance than is now the case. It is acknowledged that the difficult part of the operation is the mucosal proctectomy in which much bleeding occurs. A new modality, the surgical ultrasonic aspirator, has been demonstrated in animal work to be of use in mucosal stripping, which can be done quickly and with minimal blood loss. When applied to mucosal proctectomy, in dogs, this early promise was maintained and this part of the operation was considerably enhanced. Furthermore, the gratifying postoperative results of rapid control over the faecal stream, which is maintained, would seem to indicate that the procedure is in fact done with a minimum of trauma. Good healing was evident and no complications due to the procedure were encountered.

Acknowledgements

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References

BURNHAM W. R., LENNARD-JONES J. E. and BROOKE B. N. (1977) Sexual problems among married ileostomates. *Gut* **18**, 673–677.

FLAMM E. S., RANSOHOFF J., WUNCHINICH D. et al. (1978) Preliminary experience with ultrasonic aspiration in neurosurgery. *Neurosurgery*. **2**, 240–245.

HEIMAN T., BECK R. and GREENSTEIN A. J. (1978) Familial polyposis coli. Management by total colectomy with preservation of continence. *Arch. Surg.* **113**, 1104–1106.

HODGSON W. J. B., BAKARE S., HARRINGTON E. et al. (1979) General surgical evaluation of a powered device operating at ultrasonic frequency. *Mt Sinai J. Med.* **46**, 99–103.

HODGSON W. J. B., PODDAR P. K., MENCER E. J. et al. (1980) Evaluation of ultrasonically powered instruments in the laboratory and in the clinical setting. *Am. J. Gastroenterol.* (In the press.)

HODGSON W. J. B., PODDAR P. K., WEITZ J. et al. (1980) The Cavitron ultrasonically powered aspiration device (CUSA^{TM} System): an instrument used for selective dissection of blood vessels. In: *General Microsurgery*. Houghton Mifflin. (In the press.)

JAFFE N. S. (1978) Current concepts in ophthalmology. Cataract surgery—a modern attitude toward a technologic explosion. *N. Engl. J. Med.* **299**, 235–237.

JEFFERY P. J., HAWLEY P. R. and PARKS A. G. (1976) Colo-anal sleeve anastomosis in the treatment of diffuse cavernous haemangioma involving the rectum. *Br. J. Surg.* **63**, 678–682.

KELMAN C. D. (1969) Phaco-emulsification and aspiration. *Am. J. Ophthalmol.* **67**, 464–477.

KELMAN C. D. (1973) Phaco-emulsification and aspiration—a report of 500 consecutive cases. *Am. J. Ophthalmol.* **75**, 764–768.

KOCK N. G. (1969) Intra-abdominal 'reservoir' in patients with a permanent ileostomy: preliminary observations on a procedure resulting in faecal 'continence' in five ileostomy patients. *Arch. Surg.* **99**, 223–226.

MARTIN L. W., LECOULTRE C. and SCHUBERT W. K. (1977) Total colectomy and mucosal proctectomy with preservation of continence in ulcerative colitis. *Ann. Surg.* **186**, 477–480.

RAVITCH M. M. and HANDELSMAN J. C. (1951) One-stage resection of entire colon and rectum for ulcerative colitis and polypoid adenomatosis. *Bull. Johns Hopkins Hosp.* **88**, 59–82.

RAVITCH M. M. and SABISTON D. C. (1947) Anal ileostomy with preservation of the sphincter. *Surg. Gynecol. Obstet.* **84**, 1095–1099.

SOAVE F. (1964) Hirschsprung's disease. A new surgical technique. *Arch. Dis. Child.* **39**, 116–124.

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Modulation of the immune response and control of tumour spread by a new synthetic compound

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SUMMARY

A small molecular weight biofunctional polymer, NED 137, has been investigated for its anti-neoplastic effect. Through its effect on the immune system, particularly the induction of B cell differentiation to antibody producing cells, this synthetic compound can retard tumour growth and prevent the development of distant metastases. Reactivity to tumour developed following administration of the NED 137. No toxicity has been observed. The polymer NED 137 is now being tested in phase I and phase II clinical trials.

THE use of adjuvant stimulation to improve an immune response to tumour antigen is a goal yet unattained. Recent evidence substantiates the view that human tumours carry tumour-specific antigens as well as tumour-associated antigens (Herlyn et al., 1979). This evidence implies that manipulation of the immune system could facilitate the development of a competent immune response to tumours. It is appropriate to assume that tumour-specific antigens are relatively non-immunogenic and that an immune response could inhibit metastatic disease while having a limited effect on primary tumour growth.

This report describes the investigation of an immune modulator known as NED 137. This polymer can selectively stimulate the B cell component of the immune system and our data indicate that it is able to stimulate antibody production to tumour. The present studies demonstrate the ability of the compound to decrease local tumour growth and to prevent the development of metastases. Anti-tumour reactivity developed following the administration of NED 137. This reactivity could be transferred to normal animals by serum. A comparison of NED 137 to standard non-specific adjuvants such as *Corynebacterium parvum* and BCG will be described.

Materials and methods

The animals utilized in these experiments were 2–4-month-old Fischer strain rats (F344), supplied by Microbiological Associates, Bethesda, Maryland. Animals were maintained in single cages and fed standard rat chow and water *ad libitum*.

The tumour used was a methylcholanthrene-induced carcinoma of the bladder (FBCa) in F344 rats. A 2×2 mm trochar implanted subcutaneously grows rapidly and a 2×2 cm mass is apparent at 7–10 days after implantation. Subcutaneous FBCa consistently metastasized to the lungs; pulmonary lesions were produced by intravenous injection of 10^6 FBCa cells. Subcutaneous FBCa can be surgically excised; however, the recurrence rate after excision at 10 days post implant is 100 per cent.

The development of an immune response to tumour was monitored *in vivo* using an adaptation of Bainbridge and Gowland's (1966) method of assessing allogeneic reactions. Animals were sensitized to tumour by excision of subcutaneous FBCa or by injection of 10^6 FBCa i.v.; test animals also received NED 137 intraperitoneally at 30 mg/kg. Sensitization to tumour-specific antigens was evaluated by the survival of ^{51}Cr-labelled FBCa in test animals, i.e. decreased survival of labelled cells indicated an increased recognition and destruction of FBCa. In this manner, an index of antigen recognition was computed with test values of retention divided by control values. Therefore, a lower index correlated with a greater degree of tumour destruction.

This assay was used in the examination of the mechanism of the anti-tumour reaction that developed after administration of NED 137 to tumour-bearing animals. The cytotoxic capacity afforded normal animals as a result of the transfer of either 1×10^8 spleen cells or 5 ml of serum from animals cured of tumour was measured.

The effect of NED 137 on tumour growth was compared with the effect produced by *C. parvum* and BCG. BCG (Connaught Laboratories, Toronto, Ontario) was administered i.p. at 0·1 mg per animal. Those animals receiving *C. parvum* (Wellcome Laboratories, Beckenham) were treated with 0·75 mg i.p. and i.v. weekly for 4 weeks. All three immunostimulants were administered to test animals after excision of their subcutaneous tumour.

Results

The survival of animals with *in situ* FBCa is shown in *Fig*. 1. Animals treated with NED 137 i.p. at 30 mg/kg showed prolonged survival as compared to control animals. Of even greater significance was that all the treated animals were found to be free of pulmonary metastases when autopsied, while all the control animals had extensive pulmonary metastases.

Fig. 2 illustrates the effect of NED 137 on tumour recurrence and the development of metastases after surgical excision of the primary tumour. Control animals showed 100 per cent tumour recurrence with subsequent death of all animals by 5 weeks post excision. When these animals were autopsied, all were found to have lung metastases. Animals treated with NED 137 i.p. at 30 mg/kg at the time of excision showed no local recurrences at 60 days post excision. When sacrificed at 60 days, all treated animals were free of pulmonary metastases.

In experiments where animals treated with NED 137 were not sacrificed, it was noted that recurrent tumour began to develop at 2 months post excision. Retention of ^{14}C-NED 137 indicated that levels of this compound in various body tissues decreased substantially at 60 days after i.p. administration. Therefore, the effect of multiple doses of NED 137 on tumour growth were examined in an effort to promote a more permanent anti-tumour response. As shown in *Fig*. 3, animals that had received four consecutive doses of NED 137 i.p. at 6-weekly intervals remained tumour-free. This group of animals has now been free of tumour for more than 6 months.

To assess the anti-tumour activity of NED 137 *in vivo* we monitored the survival of ^{51}Cr-labelled FBCa cells in control animals or animals treated with NED 137 (*see* Methods). As shown in *Table I*, treated

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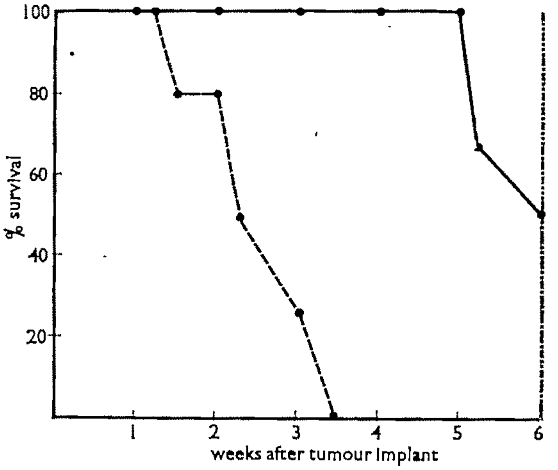

Fig. 1. The effect of NED 137 on survival with local tumour growth. Untreated control animals (● — — — ●) were dead from local tumour and metastases at a mean of 23 days after implantation. At 6 weeks after implantation, 50 per cent of the NED 137 treated animals (●——●) were still alive. These animals were sacrificed and found to be free of pulmonary metastases. ($n = 30$ for each group.)

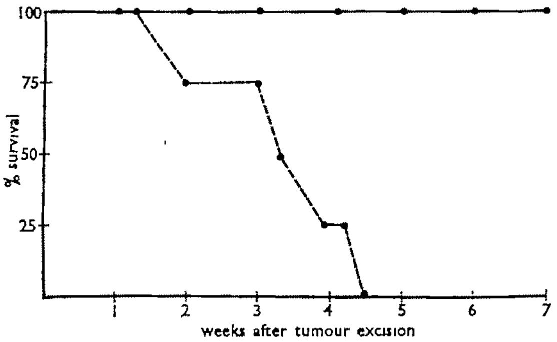

Fig. 2. The effect of NED 137 on survival after excision of local tumour. Subcutaneous tumour was excised and test animals received NED 137 at 10 days after tumour implantation. All tumours in untreated controls (● — — — ●) recurred and animals died at a mean of 35 days after excision. NED 137 treated animals (●——●) were still alive at 7 weeks after excision with no recurrence. ($n = 60$ for each group.)

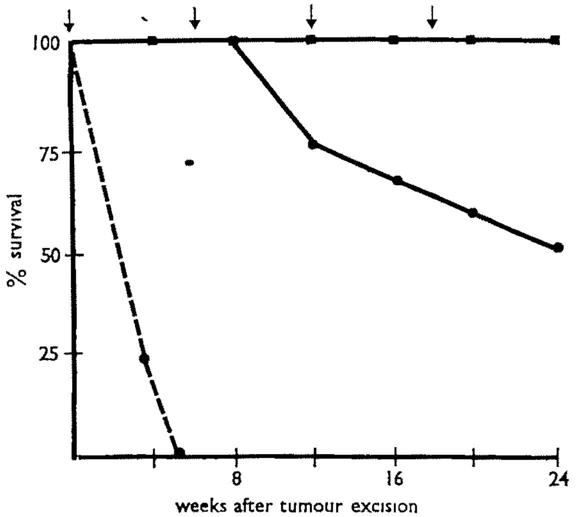

Fig. 3. The effect of NED 137 on recurrence after excision when administered every 6 weeks for 24 weeks. Untreated control animals (● — — — ●) showed recurrence and died by 5 weeks after excision. Fifty per cent of animals treated with a single dose of NED 137 (●——●) were dead from recurrent local tumour at 24 weeks after excision. Animals that received four consecutive doses of NED 137 (■——■) at 6-weekly intervals (↓) remained tumour-free. ($n = 60$ for each group.)

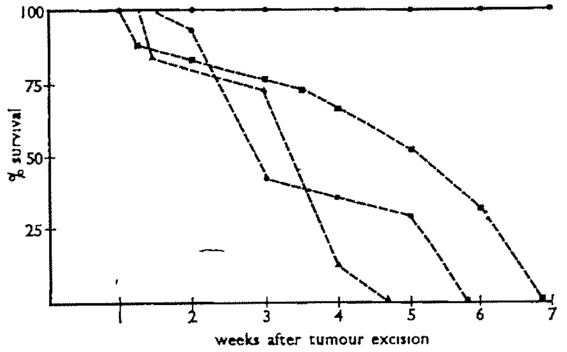

Fig. 4. The effect of NED 137 (●——●) compared with no treatment (▲), BCG (● — — — ●) and *C. parvum* (■) on tumour recurrence and survival. ($n = 10$ for each group.) (For details of administration *see* text.)

animals showed a marked increase in their capacity to destroy labelled tumour cells. *Table I* gives data obtained when cells or serum from cured animals were transferred to normal F344. The capacity to cause a significant degree of tumour cell lysis was transferred to normal animals in the 'cured' serum. Moreover, the serum component responsible for this increased destruction was precipitable by 40 per cent $(NH_4)_2SO_4$.

The efficacy of three adjuvant therapies—NED 137, *C. parvum* and BCG—on survival after tumour excision is compared in *Fig.* 4. It is apparent that NED 137 is markedly superior in prolonging survival after excision when compared with BCG or *C. parvum.*

Discussion

It should be possible to develop an effective immune response to tumour-specific antigens; however, it is exceptional to achieve this. A variety of hypotheses have been proposed to account for this inconsistency. It is apparent that both specific and non-specific suppression of the immune system can occur in the course of tumour development. It has been suggested that blocking factors in serum—either soluble tumour antigen or antigen-antibody complexes—interfere with potentially cytotoxic T cells capable of destroying tumour cells (Sjögren et al., 1971; Baldwin et al., 1973). Recent assessment of these findings suggests that these blocking factors could be non-specific.

Recently, particular emphasis has been placed on thymus-derived specific suppressor cells which are capable of suppressing an anti-neoplastic reaction, and manipulations to eliminate suppressor T cells have been examined. In these cases an enhanced response to the tumour antigen has been observed (Falk et al.,

Table I: ESTIMATION OF *IN VIVO* LYSIS OF ^{51}Cr-LABELLED TUMOUR CELLS

Treatment	Cpm/g (mean±s.e.mean)	Index
Nil	1362±41	1·00
FBCa	1321±78	0·97
NED	1348±85	0·99
FBCa+NED	572±61	0·42*
Transfer of:		
Normal cells	1268±39	0 93
Normal serum	1346±74	0·99
Cured cells	1294±62	0·95
Cured serum	898±28	0·55*
Cured serum precipitate	885±35	0·64*
Cured serum supernatant	1267±63	0·93

* $P<0·001$.

Animals with tumour only or NED 137 only showed no difference of recognition and destruction of tumour cells as compared with untreated rats. Tumour-bearing animals treated with NED 137 showed a significant increase in the destruction of tumour cells. Transfer of 'cured' serum to normal animals was able to effect a similar increase in tumour cell destruction. Comparable lysis of tumour cells was affected by the ammonium sulphate precipitate of the 'cured' serum but not from the supernatant or by the cells from 'cured' animals. ($n=5$ for each group.)

1978). It should be possible to obtain an effective anti-tumour response if a particular subpopulation of lymphoid cells could be stimulated selectively, thereby circumventing the T-cell system and, in particular, its suppressor component. The most likely candidate for B cell stimulation would be polyclonal activators as described by Möller (1977). These substances are B cell mitogens and stimulate B cells to effect enhanced antibody production. However, polyclonal activators can lead to the development of auto-antibodies (Primi et al., 1977).

NED 137 can enhance the number of antibody producing cells to non-allogeneic particulate antigens *in vivo*. No *in vitro* mitogenic effect was detectable and no auto-antibody has been demonstrable after *in vivo* use (Falk et al., 1979).

It is apparent from these studies that this polymer can promote a dramatic anti-tumour response. This response is transferred to normal animals by the serum of animals treated with NED 137. In treated animals, significant retardation of tumour growth and prevention of metastases is achieved. Toxicity experiments have shown that NED 137 has no acute or chronic toxicity in experimental animals. On this basis, a phase I study of advanced gastrointestinal malignancy was initiated in February 1979. No toxicity has been observed to date and early results from this study are promising.

In conclusion, a new polymer capable of specific stimulation of the immune response has been developed. As it is just one compound representing a family of polymeric compounds, it should be considered as the prototype of immune stimulants which specifically activate subpopulations of the immune system.

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R. E. Falk is an Associate of the Medical Research Council of Canada.

References

BAINBRIDGE D. R. and GOWLAND G. (1966) Detection of homograft sensitivity in mice by the elimination of chromium-51-labelled lymph node cells. *Ann. NY Acad. Sci.* **129**, 257–273.

BALDWIN R. W., PRICE M. R. and ROBINS R. A. (1973) Significance of serum factors modifying cellular immune responses to growing tumours. *Br. J. Cancer* **28**, (Suppl. 1), 37–47.

FALK R. E., NOSSAL N. A. and FALK J. A. (1978) Effective anti-tumor immunity following elimination of suppressor T cell function. *Surgery* **84**, 483–489.

FALK R. E., NOSSAL N. A., MAKOWKAL et al. (1979) Chemical modulation of immune response to tumour associated antigen. In: LEVY J. (ed.) *Proceedings of the International Congress on T Cell Regulation.* Vancouver, UBC Press.

HERLYN M., STEPLEWSKI Z., HERLYN D. et al. (1979) Colorecta carcinoma-specific antigen: detection by means of monoclonal antibodies. *Proc. Natl Acad. Sci.* **76**, 1438–1442.

MOLLER G. (1977) Mechanism of B-cell activation and self-non-self discrimination. *Cold Spring Harbor Symp. Quant. Biol.* **41**, Pt 1, 217–226.

PRIMI D., SMITH E., HAMMARSTRÖM L. et al. (1977) Polyclonal B-cell activators induce immunological response to autologous serum proteins. *Cell. Immunol.* **34**, 367–375.

SJÖGREN H. O., HELLSTROM I., BANSAL S. C. et al. (1971) Suggestive evidence that the 'blocking antibodies' of tumor-bearing individuals may be antigen-antibody complexes. *Proc. Natl Acad. Sci.* **68**, 1372–1375.

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The effect of epidural analgesia on postoperative sodium balance

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SUMMARY

The effect of a high epidural blockade on postoperative sodium (Na) retention has been studied in 8 patients undergoing cholecystectomy, with a further 8 patients, who received conventional anaesthesia and analgesia, acting as a control group. Preoperatively, all the patients received 90 mmol of Na per day and were in Na balance at the start of operation; this intake was continued for 48 h after the operation by intravenous infusion, and the epidural blockade was maintained with regular supplements of bupivacaine throughout. In addition to urine Na excretion and blood pressure changes, plasma levels of aldosterone, cortisol, renin activity and glucose were measured at appropriate intervals.

The Na retention in both the epidural and control groups was the same (139 mmol and 135 mmol respectively at 48 h), but there were significant differences in the measurements of all the other factors. It is concluded that the epidural was providing effective blockade, but that the factors which cause Na retention were not affected by the epidural blockade. These results are at variance with another study of the effect of epidural blockade on postoperative Na retention (Bevan, 1971), and the possible reasons for this are discussed.

SODIUM (Na) retention is one of the most constant features of the metabolic response to surgery, with approximately two-thirds of any postoperative Na intake being retained 48 h after a major operation. The cause of this Na retention is still unclear, but it seemed that an important advance in our understanding might have been made when Bevan (1971) reported that postoperative Na retention was abolished if a high thoracic epidural blockade was given. Bevan's study was carried out on 18 male patients undergoing vagotomy and pyloroplasty; all received a general anaesthetic and 8 were given, in addition, an epidural block, maintained for 48 h, from the fourth to the twelfth thoracic segments; 6 of the epidural group had a net Na loss over this 48 h, although their water balance was the same as the control group.

Although this reported effect of epidural analgesia has not been re-examined until now, many other studies of the effects of epidural blockade in the perioperative period have been carried out; it has been shown that an epidural block will delay the plasma cortisol response to surgery (Lush et al., 1972; Gordon et al., 1973; Cosgrove and Jenkins, 1974), will diminish the usual rise in blood glucose (Bromage et al., 1971; Brandt et al., 1976; Madsen et al., 1977), reduce the negative nitrogen balance (Brandt et al., 1978) as well as affecting the initial postoperative changes in fibrinolysis (Engquist et al., 1976). Thus it seems that epidural blockade may have a fundamental effect in modifying many of the metabolic and endocrine responses to surgery, possibly by interrupting painful stimuli from the operation site. However, Bevan's later explanation (Bevan, 1973) of the effect of epidural blockade on Na retention was that it was due to blocking of the sympathetic outflow to the kidney, rather than pain impulses from the wound.

This present study was designed to re-evaluate the effect of epidural blockade on postoperative sodium retention. Two groups of patients each received a standard general anaesthetic but one group was given a high epidural blockade in addition, maintained for 48 h. As well as following the Na balance, measurements were made of plasma cortisol and glucose changes to assess the effectiveness of the nerve block, and of the plasma aldosterone and renin changes to obtain further information concerning their possible role.

Patients and methods

Patients undergoing elective cholecystectomy were studied, and were excluded from the study if they had had any recent acute inflammation of the gallbladder, if they had any cardiovascular, endocrine or renal disease or if they were unwilling to give their informed consent to the study.

For 3 days before the operation the patients were given a diet containing 90 mmol each of Na and K daily, for accuracy low salt foods being supplemented with Slow-Na and Slow-K tablets, the last of any such supplements being given 24 h preoperatively. Urine collections were carried out over this period and patients were excluded from the study if their urinary Na output on the day before operation differed by more than 30 mmol from the intake on this day. The study was terminated when 16 complete investigations (8 in the control and 8 in the epidural group) had been achieved.

All operations started at approximately 0900 h. Premedication, usually methadone 10 mg and atropine 0·6 mg, was given at 0730 h and general anaesthesia induced at 0830 h with thiopentone; a muscle relaxant (usually d-tubocurarine, occasionally supplemented with suxamethonium) was given, the vocal cords were sprayed with local anaesthetic and an endotracheal tube passed. The patients in the epidural group then had a Lee Tuohy epidural cannula inserted into the T7–8 interspace and an epidural catheter passed, blockade being carried out with 10 ml of 0·5 per cent bupivacaine, the start of the operation being delayed 20 min to allow the bupivacaine to act. Blood pressure was measured at frequent intervals in all patients. Blood loss during the operation was measured by swab weighing.

At the start of operation an intravenous infusion was set up and all patients received, in each 24-h period, 3 l of water, 90 mmol of Na and 120 g of glucose in the form of 3 l of one-fifth normal saline in dextrose 4·5 per cent. No potassium was given and no oral fluids were allowed during the first 48 h after operation.

Postoperatively, analgesia in the epidural group was maintained for 48 h by injections of bupivacaine 0·5 per cent into the epidural catheter so that the band of analgesia extended from T4 to T12 dermatomes throughout this period. No difficulty was found in keeping all 8 patients completely pain-free, and although all of them had a fall of blood pressure following blockade no special corrective action was needed in any of them. Patients in the control group were given methadone 10 mg p.r.n. for analgesia, and patients in both groups were kept in bed throughout the 48 h study period. None of

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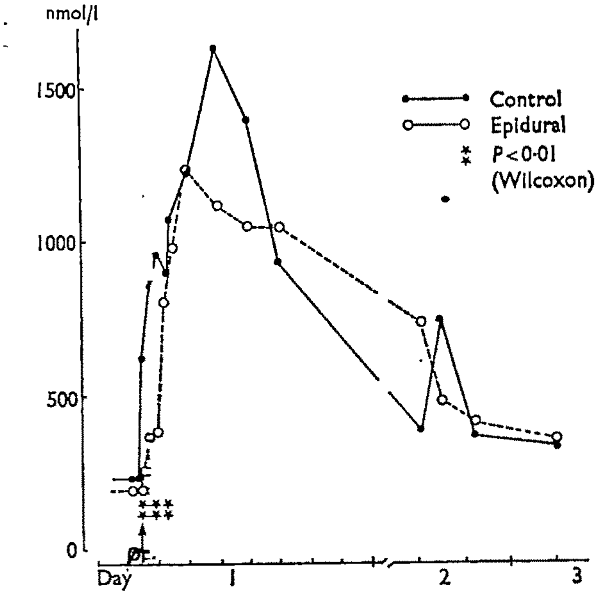

Fig. 1. Plasma cortisol changes.

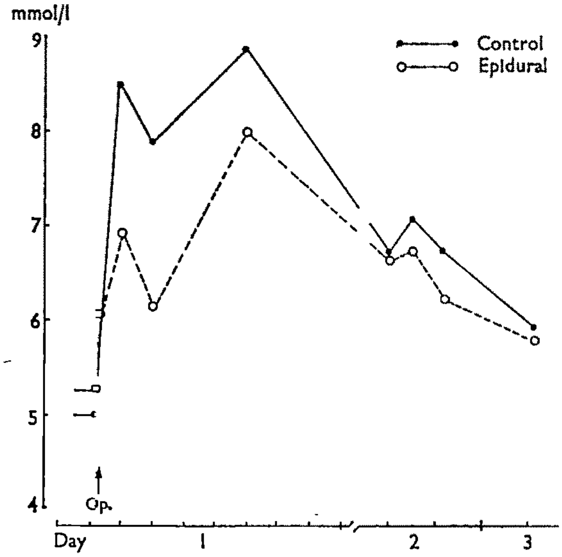

Fig. 2. Plasma glucose changes.

the patients developed fever or any other complication in the postoperative period. No patient had a nasogastric tube passed and none had any significant extrarenal losses.

Urine was collected from all patients by bladder catheter which was passed immediately after induction of anaesthesia, and the urine volume, Na and K concentrations measured. Blood samples were collected via a plastic cannula inserted into a cubital fossa vein after the premedication had been given; samples were drawn at 0825 h, 0835 h (immediately after induction of general anaesthesia), 0900 h, 0930 h, 1000 h, 1030 h, 1100 h, 1200 h, 1400 h, 1800 h on the operation day, at 0830 h, 1200 h and 1800 h on the first postoperative day and at 0830 h on the second postoperative day. On each of these samples the following measurements were made: haematocrit (Hawkesley microhaematocrit); plasma proteins (Vickers auto analyser); Na and K concentrations (Vickers auto analyser); plasma aldosterone (radioimmunoassay by a modification of the method of Jowett et al., 1973); plasma renin activity (Menard and Catt, 1972); plasma cortisol (Corning cortisol radioimmunoassay kit); plasma glucose (Vickers auto analyser). The aldosterone, renin and cortisol assays had an interassay variability of 8, 2–9 and 7 per cent respectively, and an intra-assay variability of 6, 2–3 4 and 5 per cent. The total blood taken for analysis over the 48-h period was 160 ml in each patient. Apart from the Vickers auto analyser, all analyses were carried out in duplicate. The significance of the data was analysed by means of the Wilcoxon rank test.

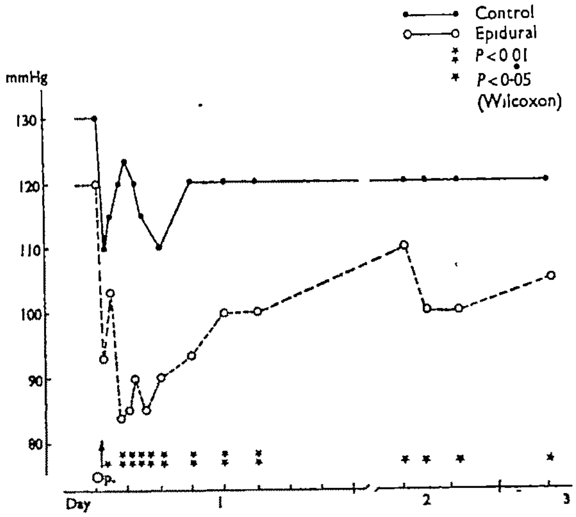

Fig. 3. Systolic blood pressure changes.

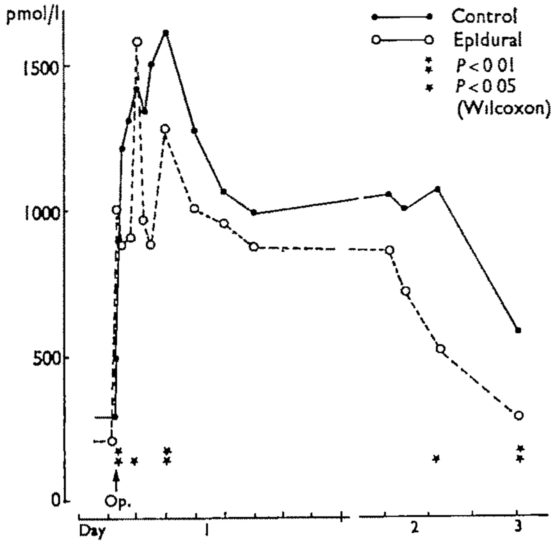

Fig. 4. Plasma aldosterone changes.

Results

Details of the patients in the two groups are shown in *Table I;* both groups are similar in median age, weight, height, duration of operation and operative blood loss.

Plasma cortisol (Fig. 1)

In the epidural group the cortisol response was delayed, the 0900 h, 0930 h and 1000 h samples being

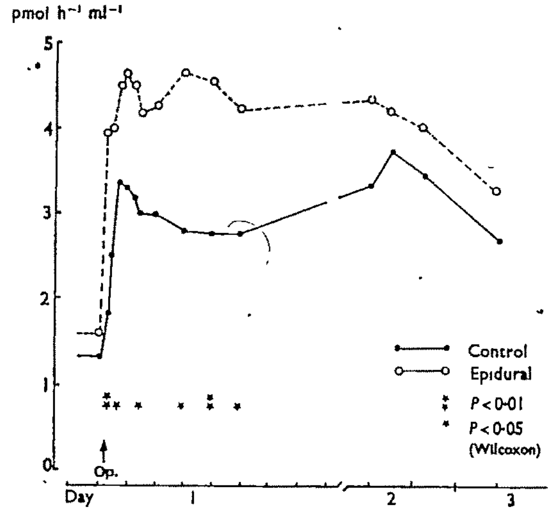

Fig. 5. Plasma renin activity changes.

Table I: PATIENTS STUDIED

Case no.	Sex	Age (yr)	Weight (kg)	Height (cm)	Operation duration (min)	Blood loss (ml)
Control group						
1	F	49	61	175	95	300
2	F	43	61	165	65	160
3	F	53	76	160	48	160
4	M	50	82	190	120	210
5	F	42	64	163	90	300
6	F	32	55	163	60	110
7	F	68	67	165	25	90
8	F	46	68	170	95	110
Median values		48	66	165	78	160
Epidural group						
9	F	35	61	165	80	130
10	F	34	56	157	75	160
11	M	58	78	178	80	220
12	M	71	48	165	95	200
13	F	47	67	170	60	90
14	F	25	64	173	90	80
15	F	61	57	173	60	100
16	F	39	60	170	75	140
Median values		43	61	170	78	135

Table II: CUMULATIVE SODIUM BALANCES (mmol)

Case no.	24 h	48 h
Control group		
1	+69	+132
2	+55	+119
3	+85	+169
4	+62	+88
5	+87	+162
6	+69	+143
7	+82	+161
8	+50	+135
Median values	+69	+139
Epidural group		
9	+59	+106
10	+69	+121
11	+68	+146
12	+83	+161
13	+75	+153
14	+59	+123
15	+81	+168
16	+51	+29
Median values	+69	+135

significantly lower than those in the control group ($P<0{\cdot}01$ in each case). After this initial difference both groups had similar responses, both rising to a peak of between 6 and 7 times the basal preoperative concentration.

Plasma glucose (*Fig. 2*)

The median value of the epidural group was less than that of the control group at each sampling time after the start of operation, and although there was no significant difference between the groups at any one sampling time, the difference in median values over the whole period is significant on the sign test ($P<0{\cdot}05$).

Blood pressure (*Fig. 3*)

Although there was a fall in pressure in all patients studied, this fall was considerably greater in the epidural group, the pressures here being significantly lower than in the control group from just after the epidural was established until the end of the study period.

Sodium balance (*Table II*)

Both groups retain just over two-thirds of their Na intake at 48 h.

Plasma aldosterone (*Fig. 4*)

In the epidural group the initial response was more abrupt, and was significantly greater than in the control group just before the skin incision was made. Also the peak response occurred earlier in the epidural group, at the 1000-h sample (a 7·5-fold increase in median values) whereas the peak occurred at the 1200-h sample in the control group (a 5·4-fold increase). Over the remainder of the study period the response was smaller in the epidural group.

Plasma renin (*Fig. 5*)

The response was more abrupt in the epidural group, the values for the 0835-h and 0900-h samples being significantly higher than in the control group: the peak response on the operation day occurred later in the epidural group (a 2·9-fold rise at the 1400-h sample) than in the control group (a 2·5-fold rise at the 0930-h sample). The differences between the groups were not significant after the operation day.

Discussion

Before comparing the Na excretion results in our two groups of patients, it is necessary to determine that the epidural blockade was in fact effective throughout the study period. Clinical observations suggested that this was the case, because as soon as the patients recovered consciousness after the operation careful skin testing was carried out, and the band of analgesia was maintained from the T4 to T12 dermatomes by giving additional bupivacaine. Further evidence that the epidural blockade was effective is provided by the blood pressure readings and the plasma glucose and cortisol changes. The blood pressure in the epidural group was significantly lower throughout the period of study. The cortisol response was delayed in the epidural group, and although it was only delayed for a few hours, this result is very similar to that found in other studies (Lush et al., 1972; Gordon et al., 1973; Cosgrove and Jenkins, 1974); similarly the suppression of the hyperglycaemic response is very similar to that found by other workers (Bromage et al., 1971; Brandt et al., 1976; Madsen et al., 1977). On the basis of this evidence it seems reasonable to conclude that there was an effective blockade throughout the period of study.

The results show that there was no difference in Na balance in the two groups of patients, although there were slight, but significant, differences in the changes in plasma levels of renin and aldosterone; the greater rise of plasma renin in the epidural group was probably caused by the greater fall of systemic blood pressure in this group.

Our Na balance results are at variance with those of Bevan (1971). The reason for this is not immediately apparent. In that Bevan found a difference between his two groups of patients whereas we did not, it might be argued that in our study the epidural blockade was not effective. However, for the reasons given we believe that in our patients the epidural was effective. There are many differences in the methods used in the two studies. In our study the same fluid intake of approximately 2·8 mmol Na kg^{-1} 48 h^{-1} was used in all patients; from the diagram Bevan gives showing Na balance it would appear that his intakes ranged from 1·3 to 7·0 mmol Na kg^{-1} 48 h^{-1}, and fluids were given at different rates during and after the operation. There is also an important difference in the calculations of the Na balance since Bevan's Na output data include renal and gastrointestinal losses, but our patients had no significant extrarenal losses.

Other differences between the two studies are that Bevan's patients were males undergoing vagotomy and pyloroplasty whereas most of our patients were female and were undergoing cholecystectomy. Furthermore, all our patients were maintained on the same Na intake before surgery and were in Na balance at the start of the operation; in our patients the epidural blockade was maintained with plain bupivacaine whereas Bevan used bupivacaine with adrenaline. Bevan gives no details of whether his control group of patients was kept to the same degree of immobility and bed rest as the epidural patients, nor of the blood pressure changes in his two groups. However, in spite of these differences in methods used we are unable to explain the fundamental differences in the Na balance in these two studies.

In conclusion, in this present study high epidural blockade was found to have no effect on Na retention in patients undergoing uncomplicated cholecystectomy and receiving 90 mmol of Na daily; confirmation was found, however, of the delay of the cortisol response and reduction of the hyperglycaemic response to surgery by the epidural.

Acknowledgements

We are grateful to Drs I. Verner, J. Hulf and G. Grundy for their skilled administration of anaesthesia to these patients, to our ward sisters for their collaboration in the study, to Mrs N. Payne who performed the renin assays and to the staff of the Courtauld Institute of Biochemistry for their help in some of the estimations. We are also indebted to Professor L. P. Le Quesne for his advice and encouragement.

References

BEVAN D. R. (1971) Modification of the metabolic response to trauma under extradural analgesia. *Anaesthesia* **26**, 188–191.

BEVAN D. R. (1973) The sodium story: effects of anaesthesia and surgery on intrarenal mechanisms concerned with sodium homeostasis. *Proc. R. Soc. Med.* **66**, 1215–1220.

BRANDT M. R., FERNANDES A., MORDHORST R. et al. (1978) Epidural analgesia improves postoperative nitrogen balance. *Br. Med. J.* **1**, 1106–1108.

BRANDT M. R., KEHLET H., BINDER C. et al. (1976) Effect of epidural analgesia on the glycoregulatory endocrine response to surgery. *Clin. Endocrinol.* **5**, 107–114.

BROMAGE P. R., SHIBATA H. R. and WILLOUGHBY H. W. (1971) Influence of prolonged epidural blockade on blood sugar and cortisol responses to operations upon the upper part of the abdomen and the thorax. *Surg. Gynecol. Obstet.* **132**, 1051–1056.

COSGROVE D. O. and JENKINS J. S. (1974) The effects of epidural anaesthesia on the pituitary–adrenal response to surgery. *Clin. Sci. Mol. Med.* **46**, 403–407.

ENGQUIST A., ASKGAARD B. and FUNDING J. (1976) Impairment of blood fibrinolytic activity during major surgical stress under combined extradural blockade and general anaesthesia. *Br. J. Anaesth.* **48**, 903–906.

GORDON N. H., SCOTT D. B. and ROBB I. W. P. (1973) Modification of plasma corticosteroid concentrations during and after surgery by epidural blockade. *Br. Med. J.* **1**, 581–583.

JOWETT T. P., SLATER J. D. H., PIYASENA R. D. et al. (1973) Radioimmunoassay of aldosterone in plasma and urine: validation of a novel separation technique and a rapid urine assay. *Clin. Sci. Mol. Med.* **45**, 607–623.

LUSH D., THORPE J. N., RICHARDSON D. J. et al. (1972) The effect of epidural analgesia on the adrenocortical response to surgery. *Br. J. Anaesth.* **44**, 1169–1172.

MADSEN S. N., BRANDT M. R., ENGQUIST A. et al. (1977) Inhibition of plasma cyclic AMP, glucose and cortisol response to surgery by epidural analgesia. *Br. J. Surg.* **64**, 669–671.

MENARD J. and CATT K. J. (1972) Measurement of plasma renin activity concentration and substrate in rat plasma by radioimmunoassay of angiotensin I. *Endocrinology* **90**, 422–430.

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Multi-element analysis of the living body by neutron activation analysis—application to critically ill patients receiving intravenous nutrition

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SUMMARY

Neutron activation analysis has been used to determine the total content in the body of N, K, Na, Cl, P and Ca in 25 critically ill surgical patients before and after a 14-day course of intravenous nutrition. Muscle elemental composition was also determined in these patients at the same time as the total body analysis.

Over the 14-day period of intravenous feeding the total body contents of all the measured elements increased (2–9·7 per cent) but only the increase in K was statistically significant. Muscle chemistry suggested an intracellular K depletion which was corrected over the study period. The results of the total body multi-element analysis were interpreted to show a mean gain of 1·25 l of extracellular fluid and 0·51 l of intracellular fluid and direct measurement of total body water suggested that this interpretation was probably valid.

The first application of the technique to patients with nutritional and metabolic problems has quantified the weight gained by two body compartments during a 2-week period of intravenous nutrition. Its further application should help to solve a number of nutritional and metabolic problems in clinical surgery.

MANY hospital patients have abnormalities of body composition as a result of disease, trauma or sepsis. If the causes of these abnormalities are to be investigated it is important to be able to study the body composition of sick patients in as much detail as possible.

Traditional techniques for studying gross body composition, such as the measurement of body density by underwater weighing, are often unsuitable for clinical use. Dilution techniques for measuring body spaces can be used clinically, and give valuable information, but in at least some cases there is doubt as to what proportion of the total space is exchangeable (Chamberlain et al., 1968; Boddy et al., 1973).

In recent years, a new technique has been introduced which makes it possible to measure the total body contents of several elements. The technique is *in vivo* neutron activation analysis (Anderson et al., 1964). The body is irradiated with fast neutrons, some of which collide with nuclei of atoms in the body. Nuclear reactions then take place, and the reaction products are often radioactive nuclei. As they decay, these nuclei emit penetrating gamma rays which may escape from the body to be detected by external radiation counters. The energies of the gamma rays are characteristic of the nuclei which emitted them, and the resulting gamma ray spectrum can be analysed to give the body contents of several elements.

We have developed this technique into a clinically acceptable procedure which gives the body contents of N, Na, Cl, P and Ca as outlined above, and the content of K by virtue of its natural radioactive constituent, ^{40}K (Burkinshaw, 1978). The method appears capable of giving valuable new information about body composition in a variety of diseases, but its true value can be established only by its performance in actual clinical investigations. Therefore, over the past year, we have added it to our clinical procedures, and we now report our initial results on a group of 25 patients receiving intravenous nutrition.

Patients and methods

Clinical details of the 25 patients are given in *Table 1*. They were selected as follows: during 1978, 52 critically ill surgical patients were referred for intravenous feeding. All were studied according to the protocol described below. Of those who received an uninterrupted 14-day course of intravenous nutrition and gained wieght, 25 consented to muscle biopsy. These are the patients included in this report.

Intravenous nutrition was given for at least 15 days through a catheter placed in the superior vena cava according to the technique of Dudrick et al. (1970). The nutrient solution was a mixture of synthetic amino acids and dextrose with minerals and vitamins: equal volumes of Freamine II (McGaw Laboratories) and 50% dextrose to which 40–50 mmol of sodium, 20–40 mmol of potassium, 8–15 mmol of magnesium and 12–18 mmol of phosphorus were added per litre. Each 1000 ml of solution gave 42·5 gN and 1006 kcal. There were no complications attributable to the course of intravenous nutrition in any of the patients.

Vitamins were given as one daily ampoule of a multivitamin preparation (Multibionta, Merck Laboratories) and appropriate intramuscular doses of folate, vitamin K and vitamin B_{12}. The group received an average ($\bar{x} \pm$ s.d.) of 45·6 ± 11·3 kcal kg^{-1} d^{-1} and 0·30 ± 0·08 gN kg^{-1} d^{-1} (*Table 1*).

Body weight, body fat, total body water and the total body contents of N, K, Na, Cl, P and Ca were measured before intravenous nutrition and again 14 days later while intravenous nutrition was continuing. At the same times muscle and venous blood samples were taken and the concentrations of N, K, Na and Cl were determined in the extracellular and intracellular fluid of muscle.

Skinfold thicknesses were measured at the biceps, triceps and subscapular sites, using Holtain skinfold calipers. Three measurements were made at each site and the mean values used to calculate total body fat from the equations of Durnin and Womersley (1974). Total body water was calculated from the dilution in the body of 100 μCi of tritiated water given intravenously. A plasma sample was taken between 3 and 5 h after injection and duplicate aliquots of the plasma sample and appropriate standards were added to a NE260 (Nuclear Enterprises (GB) Ltd) scintillator and measured on a liquid scintillation counter. Pre-dose background plasma samples were taken before the second administration for the measurement of the remaining radioactivity.

Total body N, Na, Cl, P and Ca were measured by *in vivo* neutron activation analysis. Each patient was irradiated bilaterally with 14 MeV neutrons from a sealed tube neutron generator. Patients 3, 5, 16, 18, 19, 20, 21, 23 and 25 received a total surface dose equivalent (neutrons and γ-rays) of

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Table I: CLINICAL DETAILS OF THE PATIENTS

Patient	Weight (kg)	BW as % of ideal BW	Diagnosis	Operation	Remarks	Intravenous nutrition	
						kcal kg^{-1} d^{-1}	gN kg^{-1} d^{-1}
1 (72; M)*	53	85	Carcinoma rectum	Abdomino-perineal resection	Postoperation intravenous nutrition: moderate sepsis	38	0·25
2 (44; F)	48	78	Pancreatitis	—	Moderate sepsis	58	0·39
3 (37, F)	55	90	Mesenteric thrombosis	Small bowel resection	Severe sepsis	46	0·30
4 (46; F)	43	73	Carcinoma stomach	Subtotal gastrectomy	Intravenous nutrition for postoperative ileus	42	0·28
5 (59; M)	48	71	Carcinoma stomach	Total gastrectomy	Postoperation intravenous nutrition	46	0·31
6 (31; F)	48	73	Ulcerative colitis	—	Remission after 16 days	41	0·28
7 (63; F)	43	71	Pancreatitis	—	Moderate sepsis	55	0·37
8 (63; F)	50	87	Post-vagotomy diarrhoea	Reversed jejunal loop	No sepsis	54	0·36
9 (51; F)	77	92	Ulcerative colitis	—	Remission after 26 days	29	0·19
10 (44; M)	50	72	Pancreatitis	—	Moderate sepsis	36	0·24
11 (50; F)	50	101	External small bowel fistula	—	Spontaneous closure	42	0·28
12 (52; F)	45	78	External small bowel fistula	Surgical closure	Fed before operation	66	0·44
13 (50; M)	51	73	Gastrojejuno-colic fistula	Excision and closure	Fed before operation	41	0·27
14 (61; M)	45	67	Short gut syndrome from trauma	—	Fed for severe malnutrition	44	0·29
15 (75; M)	57	86	Carcinoma colon	Colectomy	Fed prior to surgery	28	0·18
16 (87; F)	47	80	Carcinoma stomach	Gastric resection	Fed prior to surgery	44	0·29
17 (68; M)	77	100	Pancreatitis	—	Moderate sepsis	42	0·28
18 (35; M)	64	77	Crohn's disease of small bowel	—	Fed for partial obstruction	59	0·39
19 (35; M)	46	69	Crohn's colitis	Total colectomy	Fed after surgery	67	0·45
20 (49; M)	44	67	Pancreatic fistula	—	Spontaneous closure	52	0·34
21 (37; F)	36	71	Radiation small bowel fistula	Laparotomy	Fed after surgery	41	0·27
22 (73; M)	52	68	External small bowel fistula	—	Spontaneous closure	49	0·32
23 (50; F)	35	74	Radiation small bowel fistula	Bypass of fistula	Fed prior to surgery	59	0·39
24 (39; M)	77	93	Pancreatic abscess	Total pancreatectomy	Fed after surgery	25	0·17
25 (55; F)	51	90	Carcinoma anus	Abdomino-perineal resection	Moderate sepsis	38	0·25

BW, Body weight.
* In parentheses: age in years; sex.

500 mrem, and the remainder received 50 mrem. The neutrons generate in the body short-lived radioisotopes which are specific for various body elements, and which decay with the emission of γ-rays of characteristic energies. The radiation emitted from the patient is measured in a whole body radiation counter and the complex spectrum analysed by a least squares technique to give the counting rates due to: ^{13}N (a short-lived reaction product of N), ^{24}Na, ^{38}Cl, ^{28}Al (which comes from P), ^{49}Ca and ^{40}K, which is a naturally occurring radionuclide of potassium. These counting rates are corrected for decay and variations in output of the neutron generator and the total body contents of the elements are calculated by multiplying the counting rates by appropriate calibration factors.

The precision of the measurements is a function of the radiation dose. *Table II* shows the coefficient of variation (%) obtained for each element when an anthropomorphic phantom was irradiated and measured five times at the two dose levels used in this study.

The accuracy appears to be satisfactory for clinical studies. At the higher dose the difference between the mean measured quantity of an element in the phantom and the true content ranged from 0·7 per cent for sodium to 4·3 per cent for calcium.

It would clearly have been preferable to have measured all the patients at the higher dose. However, in earlier stages of our work, we measured only potassium and nitrogen, for which the smaller dose is adequate, and this study was carried out during the period of transition to multi-element analysis using the higher dose.

The muscle samples were taken from the vastus lateralis muscle approximately 14–16 cm above the knee. Local anaesthetic (lignocaine plain, 2 per cent) was injected subcutaneously and a 1-cm incision was made into the skin and muscle fascia. The procedure of plunging the needle through the incision and sampling a piece of muscle took less than 20 s. The tissue was immediately placed in a clean plastic tube and taken to the laboratory where it was placed on a plastic sheet and rapidly freed of visible fat and connective tissue by dissection. The sample was then rolled to remove surface water, placed on aluminium foil and weighed every 15 s on a Cahn electrobalance. The rate of water loss was used to calculate by extrapolation the weight of the sample when it was removed from the container. The sample was frozen (−20 °C), freeze dried for approximately 20 h and dried to a constant weight. The water content was calculated from the weight loss. Fat was extracted from the dried sample into distilled petroleum ether (40–60) (Flear and Florence, 1961), the samples were dried and reweighed and the fat content was calculated from the weight loss.

The pieces of fat-free dry muscle were ground in an agate mortar and the powder was divided into two weighed samples, one, the larger, for electrolyte analysis and the other for nitrogen determination.

Electrolyte estimation

An accurately weighed portion of muscle powder (about 1–2 mg) was dissolved in 250 μl of 1N nitric acid and 100 μl of the solution were transferred to a small plastic pot and 20 μl of borate solution (Cotlove, 1963) were added. To the remainder of the solution (150 μl), 450 μl of water were added and two 250-μl portions of this diluted solution were removed for analysis of sodium and potassium. Sodium and potassium were measured with an EEI dual channel flame photometer, chloride was measured, after neutralization of the borate solution with 30 μl of 7·5 N nitric acid, by titration with silver nitrate using silver and mercurous sulphate electrodes as described by Bergstrom and Hultman (1974).

Nitrogen determination

Nitrogen was measured by sulphuric acid oxidation of organic nitrogen into ammonium ions which were estimated colorimetrically by an auto analyser method (Ferrari, 1960).

Water partition

The sample content of chloride was used to partition total water between the intra- and extracellular compartments (Bergstrom and Hultman, 1974).

Blood analysis

Venous blood, obtained on the same day as the biopsies, was analysed for sodium, potassium, chloride, bicarbonate, calcium, phosphate, urea, albumin and total protein.

Analytical precision

Analytical precision was estimated by taking 10 aliquots weighing between 1 and 2 mg from a solution containing ions at concentrations similar to those in muscle. The coefficients of variation were 2·3 per cent for sodium, 7·4 per cent for chloride, 2·1 per cent for potassium and for a powdered sample 8·3 per cent for nitrogen.

Table II: COEFFICIENTS OF VARIATION (%) OBTAINED WHEN AN ANTHROPOMORPHIC PHANTOM WAS IRRADIATED AND MEASURED FIVE TIMES

Dose equiv. (mrem)	K	N	Element Na	Cl	P	Ca
50	1·5	2·2	24	14	16	23
500	1·9	1·3	2·2	1·6	2·9	4·2

Table III: MULTI-ELEMENT ANALYSIS OF PATIENTS BEFORE AND AFTER 14 DAYS OF INTRAVENOUS NUTRITION

	Total body content					
	N (g)	K (mmol)	Na (mmol)	Cl (mmol)	P (mmol)	Ca (mmol)
Before	1303	2041	2789	1727	14 546	18 781
IVN	±47	±40	±498	±115	±607	±1096
After	1333	2238	3038	1828	15 053	19 152
IVN	±49	±101	±719	±74	±636	±1213
%	2·3	9·7	8·9	5·8	3·5	2·0
P	0·36	<0·001	0·11	0·29	0·35	0·75

Values are mean ± s.e. mean.

Results

The 25 patients gained an average (mean ± s.e.mean) of 2·62 ± 0·54 kg of bodyweight ($P<0{\cdot}001$); 0·55 ± 0·17 kg of body fat ($P=0{\cdot}003$) and 2·33 ± 0·55 l of water ($P<0{\cdot}001$) over the 14-day study period. The increases in the total body contents of N, K, Na, Cl, P and Ca are shown in *Table III*. *Table IV* shows the concentrations of N, K, Na and Cl in extracellular (ECF) and intracellular fluid (ICF) of skeletal muscle before and 14 days after intravenous nutrition.

The increase in total body K was associated with an increase in the concentration of potassium in both ECF (3·75 to 4·20 mmol/l, $P<0{\cdot}001$) and ICF (138·5 to 167·3 mmol/l, $P<0{\cdot}005$), but the concentrations of N, Na and Cl were not changed significantly by IVN. The changes in total body N, Na and Cl therefore reflect changes in the volumes of ECF and ICF. Let ΔE, ΔI be the mean changes in these volumes, let ΔN, ΔNa, ΔCl be the mean changes in total body N, Na and Cl and let $[N]_E$, $[Na]_E$, $[Cl]_E$ and $[N]_I$, $[Na]_I$, $[Cl]_I$ be the mean values, estimated from all the muscle samples, of the concentrations of the elements in ECF and ICF. These quantities are related by the equations:

Table IV: ELECTROLYTE AND NITROGEN CONTENTS OF MUSCLE BEFORE AND AFTER 14 DAYS OF INTRAVENOUS NUTRITION

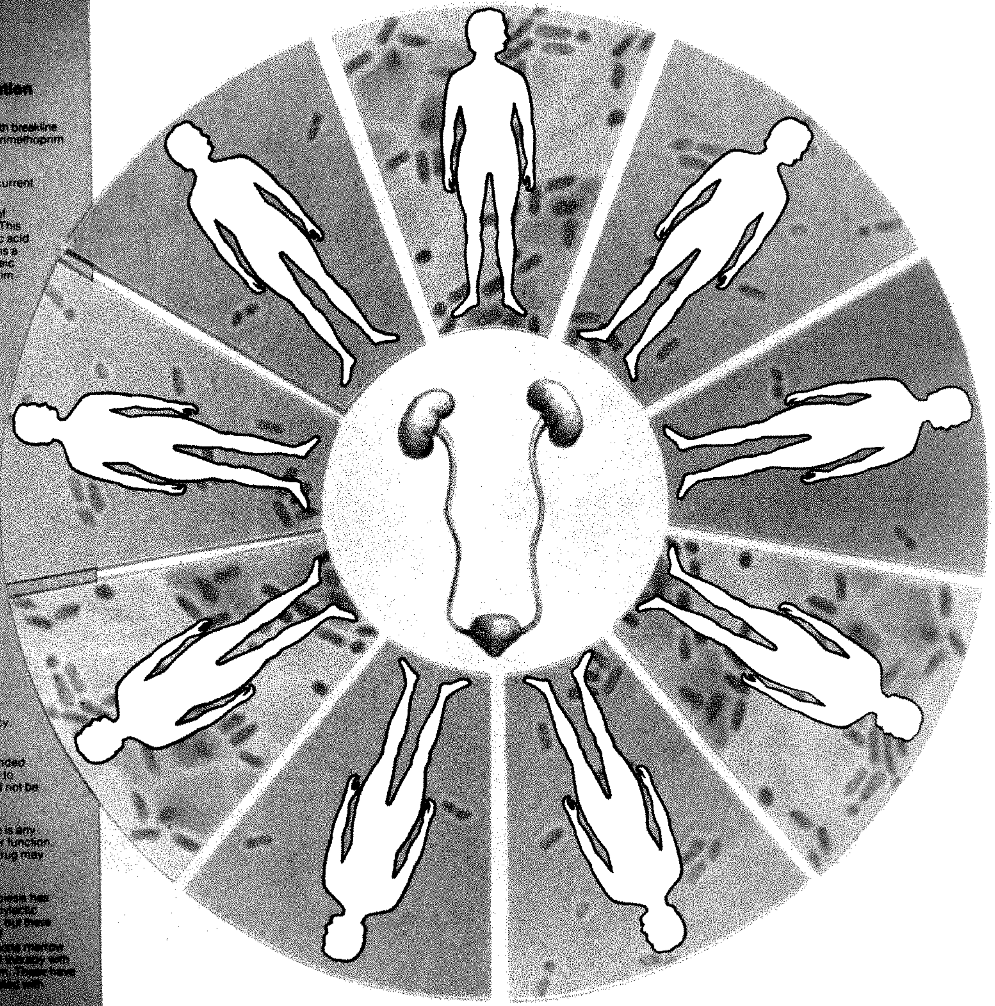
	Extracellular fluid				Intracellular fluid			
	Na (mmol/l)	Cl (mmol/l)	K (mmol/l)	N (g/l)	Na (mmol/l)	Cl (mmol/l)	K (mmol/l)	N (g/l)
Before	136·8	107·9	3·75	—	4·35	3·76	138·5	58·8
IVN	±0·9	±1·2	±0·09	—	±1·3	±0·32	±5·2	±8·1
After	137·6	109·6	4·20	—	5·89	4·22	167·3	60·0
IVN	±0·7	±0·9	±0·09	—	±3·6	±0·04	±9·4	±4·4
P	n.s.	n.s.	0·001		n.s.	n.s.	0·005	n.s.

Values are mean ± s.e. mean.

TRIMOPAN

trimethoprim

effective prophylaxis in recurrent urinary tract infection



Prescribing Information

Presentation
[illegible] diameter with breakline on reverse, each containing trimethoprim B.P. 100mg

Uses
Long-term prophylaxis of recurrent urinary tract infection.

Trimethoprim is an inhibitor of dihydrofolic acid reductase. This enzyme converts dihydrofolic acid to tetrahydrofolic acid which is a precursor of desoxyribonucleic acid. The effect of trimethoprim on folic acid synthesis is 50,000 times weaker in human cells than in bacterial cells. Trimethoprim has a range of activity very similar to that of sulphonamides but, *in vitro* most organisms show a far higher sensitivity to trimethoprim. The only coliform bacterium resistant to trimethoprim is Pseudomonas, whereas enterobacter, E. coli, Proteus and Klebsiella are trimethoprim-sensitive. Likewise trimethoprim is suitable for the therapy of Streptococcus faecalis infections. Gonococcus is trimethoprim-resistant.

Dosage and administration
Adults: For the prophylaxis of recurrent urinary tract infection, one tablet each night before bed.
Children: Paediatric dosage for prophylaxis has not been established.

Contra-indications
Serious hepatic or renal dysfunction, folate deficiency, blood dyscrasias.
Although there is no clinical evidence that the recommended dosage of Trimopan is harmful to the foetus, Trimopan should not be used in pregnancy.

Precautions
[illegible] when there is any [illegible] of kidney or liver function [illegible] accumulation of the drug may [illegible]

[illegible]

Highly active against common urinary pathogens

"The most common gram-negative bacilli, E. coli, Proteus and Klebsiella are sensitive to trimethoprim . . . Pseudomonas is resistant."(1)

Extensive clinical experience – low relapse/reinfection rates(1)

"[Trimopan] . . . has been used for more than 600,000 months of treatment, i.e. 50,000 patient years."(1)

Low incidence of resistance

"The percentage of trimethoprim-resistant strains in clinical practice has not increased remarkably during recent years."(1)

Well tolerated

". . . trimethoprim alone appears the safest of all drugs [tested] against urinary tract infection."(1)

Convenient once daily dosage

Simply – one 100mg tablet nightly.

for recurrent U.T.I.

Rx Trimopan 100mg
1 tablet at night (28)

References
(1) Kasanen et al., 1978 *Ann Clin Res* Vol **10**, supplement 22 pp5,6,28

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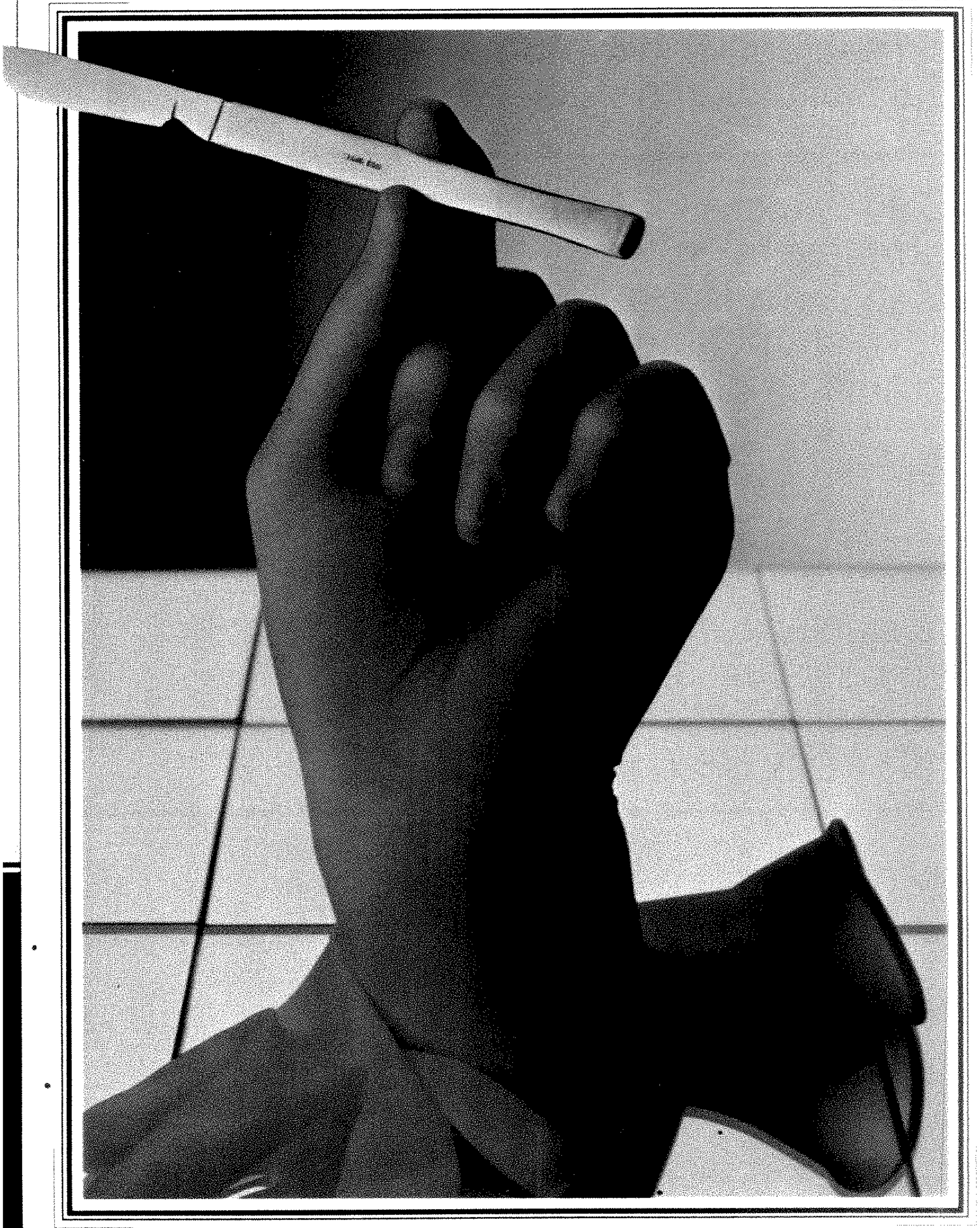

Benign Breast Disorders

3 studies on Danol

1. "...a marked improvement in both objective and subjective symptoms in 87.5% of patients studied."

(Study of 40 patients given Danol for up to 6 months. Obstet. Gynec. 1976, 48: 93.)

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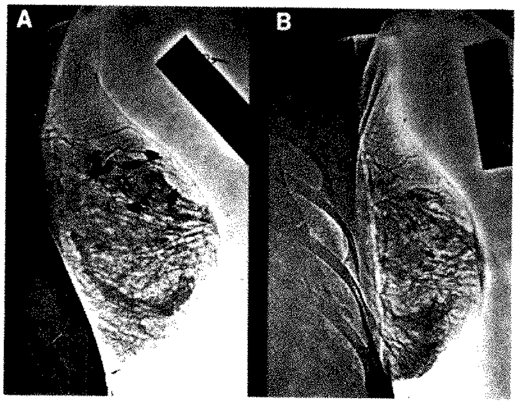
2. 75.8% "...experienced complete relief of subjective discomfort with disappearance of clinical signs."

(Study of 58 patients given Danol for between 74 and 310 days. Am. J. Obstet. Gynec. 1977, 127: 130.)



Xeromammograms of patient with intense fibrocystic disease (A) showing marked reduction in breast size and cystic area (B) after 6 months on Danol

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3. "...a significant decrease and elimination of breast pain and tenderness ...and elimination of nodules and lumpy areas..."

(Preliminary report on open study of 260 patients given Danol for 4 to 6 months. J. int. med. Res. 1977, 5 (Suppl. 3) 101-108.)

Danol
danazol

antigonadotrophic agent without oestrogenic or progestogenic activity

Danol (danazol 200 mg) PL 0071/0095. Bottles of 100 capsules. Basic NHS cost of one day's treatment £1.42 (3 capsules). **Danol-½** (danazol 100 mg) PL 0071/0094. Bottles of 100 capsules. Basic NHS cost of one day's treatment 72p (3 capsules). **Dosage** Adults 200-800 mg daily. See Data Sheet for details. **Contra-indications** Pregnancy. **Precautions** 1. Because of fluid retention, use with care in patients with cardiac or renal dysfunction, epilepsy or migraine. 2. In hepatic dysfunction. 3. Danol may potentiate the action of anticoagulants. 4. Discontinue if signs of virilisation develop. **Side Effects** Androgenic side effects (acne, oily skin, fluid retention, hirsutism, clitoral hypertrophy, voice changes, flushing and reduction in breast size) occur occasionally. Nausea, headache, dizziness, rash, nervousness, vertigo, emotional lability, backache, skeletal muscle spasm and hair loss have also been reported. Danazol has little overall effect on libido and thrombo-embolic complications have not been reported. Any increase in weight which occurs may respond to dietary control. Danol is a trade mark. Clinical reports and full prescribing information available on request from **Winthrop Laboratories**, Surbiton-upon-Thames, Surrey.

WINTHROP

$$[N]_E \Delta E + [N]_I \Delta I = \Delta N \quad (1)$$
$$[Na]_E \Delta E + [Na]_I \Delta I = \Delta Na \quad (2)$$
$$[Cl]_E \Delta E + [Cl]_I \Delta I = \Delta Cl \quad (3)$$

Since there are three equations but only two unknowns (ΔE, ΔI), and since ΔN, ΔNa and ΔCl are measured with error, the equations have no unique solution, but estimates of ΔE and ΔI can be calculated by the method of weighted least squares (Topping, 1962). The calculation gives the increase in ECF as 1·25 ± 0·67 l and the increase in ICF as 0·51 ± 0·52 l. The sum of these (1·76 l) agrees with the mean gain in total body water measured by tritium dilution (2·33 ± 0·55 l).

Discussion

In this first application of multi-element *in vivo* neutron activation analysis to studies of critically ill surgical patients, the technique has made it possible to quantify the changes in two compartments of the fat-free mass. The results suggest that the technique will be of real value in the elucidation and treatment of difficult metabolic and nutritional problems. We have already used neutron activation analysis to measure total body nitrogen directly in a wide variety of very ill surgical patients (Hill et al., 1978; Collins et al., 1979) and the results obtained have given us valuable information on the tissue composition of the weight lost after surgery (Hill et al., 1978) and on the tissue composition of the weight gained with intravenous nutrition (Hill et al., 1979) and with an elemental diet (Yeung et al., 1979). It is not surprising therefore that this further extension of neutron activation analysis to surgical patients has yielded useful information.

Multi-element analysis of 25 ill patients receiving intravenous nutrition at the start of treatment and again 14 days later showed increases in all the elements measured over the study period, although the increase was statistically significant only for K. From the data, we estimate that ECF increased by 1·25 l and ICF by 0·5 l; the sum of these increases is in reasonable agreement with the increase in total body water measured directly, suggesting that the interpretation is probably valid.

It might be argued that, as Rudman and his colleagues (1975) have shown, similar information can be derived from detailed elemental balance studies. Neutron activation analysis is, however, a less laborious procedure, and has the great advantage that it is not subject to cumulative errors resulting from loss of excreta (Hegsted, 1976; Beisel, 1979).

The precision of the technique (*Table II*) is adequate for clinical use. Suppose, for example, that 15 patients are measured with a dose-equivalent of 500 mrem, at the beginning and end of a 14-day period, during which they gain 4 g of nitrogen per day (56 g total). Then the mean daily change can be estimated with a standard error of ± 0·5 gN (13 per cent); the smallest mean change which could be detected with 95 per cent confidence would be 1·1 gN per day. These figures are rather optimistic because the reproducibility of measurements made on patients may not be quite as good as those made on phantoms (*Table II*), and the standard errors of the measured mean changes will be increased by biological differences between patients, but they serve as a guide.

We suggest, however, that the great importance of multi-element analysis is not that it replaces balance techniques but that it measures directly the total body contents of the major elements. The measured contents are of interest in themselves, but it also seems likely that they can be used to determine the sizes of various body compartments. The concept of body compartments is not new (Reifenstein et al., 1945). The principal subdivisions are: protoplasm which is rich in N, K and P, ECF which contains Na and Cl, bone which contains Ca, P and Na and fat which contains C and H. The interpretation of total body changes in terms of changes in these body compartments by uncritically using fixed ratios of the predominant elements within a given compartment can, however, be quite misleading in very ill patients. In the present study, for instance, the average intracellular concentration of muscle K was lower than normal (King et al., 1978) and this was corrected over the 14-day period of intravenous nutrition. Therefore the measured gain in total body K of 9·7 per cent cannot be interpreted as a gain of protoplasm.

Clearly, a great deal of work remains to be done. We hope soon to extend the scope of the analysis by introducing measurements of total body carbon, hydrogen and oxygen, and we are studying the difficult problem of relating the results of the measurements to the size and condition of body compartments.

Acknowledgements

The development and application of the neutron activation analysis technique are supported by a Medical Research Council Programme Grant to the Department of Medical Physics. The muscle chemistry work is supported by the Yorkshire Regional Health Authority.

We are grateful to Professor D. Johnston, Professor R. E. Ellis and Professor D. B. Morgan for their advice and help with this project, to Miss D. W. Krupowicz and Mr K. Brooks, who carried out the neutron activation measurements, and to Miss R. A. Siwek, who assisted with data processing.

References

ANDERSON A., OSBORN S. B., NEWTON D. et al. (1964) Neutron activation analysis in man *in vivo*. A new technique in medical investigation. *Lancet* **2**, 1201–1205.

BEISEL W. R. (1979) Metabolic balance studies—their continuing usefulness in nutritional research. *Am. J. Clin. Nutr.* **32**, 271–274.

BERGSTROM J. and HULTMAN E. (1974) Water, electrolyte and glycogen content of muscle tissue in patients undergoing regular dialysis therapy. *Clin. Nephrol.* **2**, 24–34.

BODDY K., KING P. C. and DAVIES D. L. (1973) The relationship between total body potassium and exchangeable body potassium measured at 24 hours and 44 hours after administration of ^{42}K. *Eur. J. Clin. Invest.* **3**, 188–192.

BURKINSHAW L., MCCARTHY I. D., OXBY C. B. et al. (1978) In: CROOK M. A. and JOHNSON P. (ed.) *Multi-element analysis of the Living Human Body by Neutron Activation Analysis. Liquid Scintillation Counting Incorporating Whole-body Counting and Radioimmunoassay*, vol. 5. Heyden, London.

CHAMBERLAIN M. J., FREMLIN J. H., PETERS D. K. et al. (1968) Total body sodium by whole body neutron activation in the living subject: further evidence for non-exchangeable sodium pool. *Br. Med. J.* **2**, 583–585.

COLLINS J. P., MCCARTHY I. D. and HILL G. L. (1979) Assessment of protein nutrition in surgical patients—the value of anthropometrics. *Am. J. Clin. Nutr.* **32**, 1527–1530.

COTLOVE E. (1963) Determination of the true chloride content of biological fluids and tissues. II. Analysis by simple non-isotopic methods. *Analyt. Chem.* **35**, 101–105.

DUDRICK S. J., LONG J. M., STEIGER E. et al. (1970) Intravenous hyperalimentation. *Med. Clin. North Am.* **54**, 577–589.

DURNIN J. V. G. A. and WOMERSLEY J. (1974) Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br. J. Nutr.* **32**, 77–79.

FERRARI A. (1960) Nitrogen determination by a continuous digestion and analysis system. *N Y Acad. Sci.* **87**, 792–800.

FLEAR C. T. G. and FLORENCE I. (1961) A rapid amino method for the analysis of skeletal muscle for water, sodium, potassium, chloride and fat. *Clin. Chim. Acta.* **6**, 129–135.

HEGSTED D. M. (1976) Balance studies. *J. Nutr.* **106**, 307.

HILL G. L., BRADLEY J. A., SMITH R. C. et al. (1979) Changes in body weight and body protein with intravenous nutrition. *J. Parent. Ent. Nutr.* **3**, 215–218.

HILL G. L., MCCARTHY I. D., COLLINS J. P. et al. (1978) A new method for the rapid measurement of body composition in critically ill surgical patients. *Br. J. Surg.* **65**, 732–735.

KING R. F. J. G., COLLINS J. P., MORGAN D. B. et al. (1978) Muscle chemistry of critically ill surgical patients and the effects of a course of intravenous nutrition. *Br. J. Surg.* **65**, 495–498.

REIFENSTEIN E. J., ALBRIGHT F. and WELLS S. J. (1945) The accumulation, interpretation and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus and nitrogen. *J. Clin Endocrinol. Metab.* **5**, 367–395.

RUDMAN D., MILLIKAN W. J., RICHARDSON T. J. et al. (1975) Elemental balances during intravenous hyperalimentation of underweight adult subjects. *J. Clin. Invest.* **55**, 94–104.

TOPPING J. (1962) *Errors of Observation and Their Treatment*, 3rd ed. London, Chapman & Hall (on behalf of The Institute of Physics and The Physical Society).

YEUNG C. K., SMITH R. C. and HILL G. L. (1979) The effect of an elemental diet on body composition—a comparison with intravenous nutrition. *Gastroenterology*. (In the press.)

Br. J. Surg. Vol. 66 (1979) 873–908

Abstracts

The Fourth Joint Meeting of the Surgical Research Society, the Society of University Surgeons and the European Society for Surgical Research, with the Surgical Research Society of Australasia, the South African Surgical Research Society and the Japanese Surgical Society, was held at the Nuffield Department of Surgery, University of Oxford, on 5, 6 and 7 July 1979 with Professor Herbert Duthie (President of the Surgical Research Society) in the Chair. The following papers were presented.

1. Cyclosporin A: effect and mode of action upon renal allografts in the dog and rat

W. P. HOMAN, M. FRENCH, KERYN A. WILLIAMS, P. MILLARD, T. G. DENTON, J. W. FABRE and P. J. MORRIS, *Nuffield Department of Surgery, University of Oxford, Radcliffe Infirmary, Oxford*

Cyclosporin A (Cy A), a new immunosuppressive agent, has been examined in dog and rat kidney allograft models. Experiments were designed to establish (1) optimal dosage, (2) optimal duration of treatment, (3) toxicity, (4) interaction with prednisolone, (5) mechanism of action and (6) effect on acute rejection. Kidney allografts between outbred dogs treated orally with Cy A at doses of 5 and 10 mg/d showed significant prolongation of survival with no histological evidence of rejection at day 7. Continued treatment, with the drug, however, did not prevent rejection, and was no more effective than a 14-day course at the same dose. The addition of prednisolone may augment the immunosuppressive effect. No evidence of nephrotoxicity or hepatoxicity was noted.

Treatment (daily)	No. of dogs
A. Cy A 10 mg/kg × 14 d	7
B. Cy A 5 mg/kg × 14 d	4
C. Cy A 2 mg/kg × 14 d	5
D. Cy A 10 mg/kg indefinitely	6
E. Prednisolone 1 mg/kg daily	6
F. Cy A 10 mg/kg indef. + pred.	6
G. Azathioprine + pred. (2 mg/kg) (1 mg/kg)	7
H. No treatment	4

Survival (d)	Median survival
A. 16, 17, 22, 28, 29, 36, 75	28
B. 16, 19, 22, 30	21
C. 7, 9, 9, 14, 18	9
D. 19, 22, 25, 47, (>8, >8)	24
E. 7, 7, 7, 7, 7, 8	7
F. 21, 24, >24, >29, (>7, >7)	>24
G. 9, 11, 13, 35, 45, 58, 72	35
H. 8, 8, 8, 9	8

Renal allografts from DA to Lewis rats, across a major histocompatibility barrier, survived indefinitely with no evidence of rejection, and again sharp dose–response effects were seen. The humoral response to the graft was measured by a ^{51}Cr release lymphocytotoxicity assay, and the cellular response by lymphocytic killing of ^{51}Cr-labelled thymocyte target cells. Cy A suppresses both the humoral and cellular responses to the allograft when used at optimal dosage. Even massive doses of Cy A, withheld until rejection of the graft was commencing, did not influence the course of the rejection.

Thus, Cy A is a powerful immunosuppressive agent in these models. It appears to act at the induction phase of the immune response to a renal allograft, abolishing both the humoral and cellular responses to the graft.

2. Postoperative pulmonary embolism: prevention by dextran or s.c. heparin?

U. F. GRUBER, T. BROKOP, B. EKLÖF, I. ERIKSSON, I. GOLDIE, L. GRAN, M. HOHL, T. JONSSON, S. KRISTERSSON, K. G. LJUNGSTRÖM, T. LUND, H. MAARTMAN MOE, T. SALDEEN, D. THOMSON, J. TORHORST, A. TRIPPESTAD and M. ULSTEIN, *Department of Surgery, Kantonsspital, CH-4031 Basel, Switzerland*

Both small doses of s.c. heparin as well as dextran 70 infusions have been shown to reduce the incidence of fatal pulmonary emboli as compared with no prevention. A prospective, randomized study in order to compare for the first time the two methods was initiated in 1976 with the following general surgical (S), orthopaedic (O), urological (U) and gynaecological (G) departments participating:

1. Kantonsspital, University of Basel (S, O, U, G—U. F. Gruber, M. Hohl, J. Torhorst)
2. Haukeland Sykehus, University of Bergen (S, O, U, G—L. Gran, H. Maartman Moe, A. Trippestad, M. Ulstein)
3. Sahlgrenska Sjukhuset, University of Göteborg (O—I. Goldie, T. Jonsson)
4. Lasarettet Helsingborg (S—S. Kristersson)
5. Lasarettet, University of Lund (S, U—T. Brokop, B. Eklöf, D. Thomson)
6. Lasarettet Danderyd, Stockholm (S—K. G. Ljungstrom)
7. Akademiska Sjukhuset, University of Uppsala (S, U—I. Eriksson, T. Saldeen)

The endpoint of the study was pulmonary embolism proved at autopsy. All patients were followed up for 1 month after the operation. Special attention was paid to the practical application and side effects of the two preventive methods.

We followed the protocol as it was applied in the heparin multicentre trial (Kakkar et al., 1975). Patients in the dextran group received 6 per cent Dextran 70 in saline (Macrodex) 3 × 500 ml: the first 500 ml being infused during operation, the second 500 ml on the evening of the operation day and the third 500 ml on the morning of the first postoperative day. All autopsy reports were evaluated by one pathologist (T. Saldeen).

A total of 4352 patients was admitted to the trial: 75 patients died during the first postoperative month, 38 in the dextran, 37 in the heparin group, the autopsy rate being 87 per cent in the dextran and 86 per cent in the heparin group. There were 5 fatal cases of pulmonary embolism in the dextran group and 3 in the heparin group. In 1 case in the dextran and in 3 of the heparin group the pathologist considered the pulmonary embolism to be contributory to death. There were 6 incidental findings of pulmonary embolism (e.g. pre-existing pulmonary embolism, microemboli), 2 in the dextran, 4 in the heparin group. Since the incidence of pulmonary embolism found at autopsy in both groups is about the same, it is concluded that both methods exert the same protective effect.

KAKKAR V. V., CORRIGAN T. P. and FOSSARD D. P. (1975) Prevention of fatal postoperative pulmonary embolism by low doses of heparin. *Lancet* **2**, 45–51.

3. Glomerulotubular sodium dynamics after supplemental albumin resuscitation

C. E. LUCAS, ANNA M. LEDGERWOOD and R. F. HIGGINS, *Department of Surgery, Wayne State University, Detroit, Michigan, USA*

Previous data from this laboratory demonstrated that albumin (Alb.), when added in a random fashion to a standard resuscitation regimen for hypovolaemic shock, causes renal sodium (Na) retention; the mechanism was not delineated.

Intrarenal Na dynamics, therefore, were analysed in 94 patients who received an average of 14·5 transfusions for shock; 46 patients received supplemental Alb. totalling 31 g during resuscitation and 150 g/d for 3–5 days. Renal plasma flow (C(PAH)), glomerular filtration rate (C(In)), Na and potassium (K) perfusion (Na-P and K-P), Na (Na-F) and K filtration (K-F), Na collecting duct flow (Na-CD), nephron reabsorption of Na (%Na-F) and K (%K-F), collecting duct reabsorption of Na (%Na-CD) and K excretion (KE-CD), and clearance of Na (C(Na)) and K (C(K)) were studied serially and compared by the Student *t* test.

Alb. increased serum Alb. levels (4·2 *v.* 2·9 g/dl), plasma volume (3895 *v.* 3579 ml), C(PAH), Na-P, and K-P (Table). In contrast, C(In) fell, thereby causing a significant fall in Na-F, K-F, and Na-CD (Table). The %Na-CD was greater in Alb. patients who, therefore, had a lower C(Na); increased %Na-CD paralleled a fall in KE-CD (Table).

	Alb.	Non-Alb.
C(PAH)* (ml/min)	466	411
Na-P* (mmol/l)	63·4	56·1
C(In)* (ml/min)	85	107
Na-F* (mmol/min)	11·9	14·5
Na-CD* (mmol/min)	1·8	2·2
%Na-CD* (mmol/min)	84	78
(KE/CD) (mmol/min)	0·12	0·14
C(Na) (ml/min)	1·45	2·4

Value expressed as mean; *indicates $P<0·05$.

Alb. causes a rise in perfusion but a fall in filtration of Na and K, possibly due to negative glomerulotubular Na feedback or increased oncotic pressure within the tuft. Further Na retention in the distal nephron due to NA-K exchange probably reflects a high inner medullary osmolality. This excessive Na retention promotes vascular overload with its important clinical implications.

4. Highly selective vagotomy for duodenal ulcer: the clinical results after 10 years

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HSV for duodenal ulcer (DU) in man was first described 10 years ago (Johnston and Wilkinson, 1969). The clinical results after 10½ years are presented, attention being focused on the first 100 consecutive patients (80 M, 20 F, mean age 42, length of history 9 years; PAO, 43 mmol/h) who were operated on by one surgeon, assessed 'blindly' at a follow-up (FU) clinic each year and followed for 8·5 (7–10·4) years, 38 per cent of them were hypersecretors (PAO>45 mmol/h).

In 96 per cent of patients, pre- and postoperative BAO and PAO$_{\text{pg}}$, and postoperative PAO were measured. All patients with pain after HSV were endoscoped, but those without pain were not. Six patients died during FU, none of ulcer disease, 2 emigrated and of the remaining 92, 7 were lost to FU.

Operative mortality was nil. Lesser curve necrosis was not encountered. One patient required reoperation for stasis (now Visick grade 3). The insulin test (IT), 1 week after HSV, was Hollander negative in 93 patients and late positive in 3. Mean PAO$_{\text{I}}$ − BAO was 0 mmol/h and only 4 tests were Stempien positive. None of the first 50 patients had a 'positive' IT: no patient has developed recurrent ulceration (RU) after 8–10 years. Two patients (2 per cent) developed RU: both had late positive ITs. One is Visick 1 and one Visick 4. RU was suspected at one time or another in a further 8 patients, but OGD + barium meal ± laparotomy were negative. Dumping was noted in 2 per cent (all mild), diarrhoea in 3 per cent and bilious vomiting in 3 per cent (male patients). Four patients are currently Visick grade 4.

The use of HSV has eliminated dumping, diarrhoea and bilious vomiting as clinical problems. A 2 per cent incidence of recurrent ulceration is attainable. Hypersecretors do not need antrectomy, if the vagotomy is complete. Intraoperative testing, a stimulus to the trainee, is not essential.

JOHNSTON D. and WILKINSON A. R. (1969) Selective vagotomy with innervated antrum without drainage procedure for duodenal ulcer. *Br. J. Surg.* 56, 626.

5. ^{111}Indium-labelled autologous leucocyte scan: analysis of a new diagnostic tool in postoperative sepsis

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Intra-abdominal infection is difficult to diagnose in the patient who has recently undergone gastrointestinal surgery. Physical examination may be deceptive and the currently available diagnostic techniques are not uniformly accurate and are limited in scope. We have previously described a new scanning technique in the diagnosis of infection. The patient's peripheral polymorphonuclear granulocytes (PMNs) are separated and labelled *in vitro* with ^{111}Indium. The autologous labelled PMNs are reinjected i.v. and whole body scanning carried out in 24 h. Radioactivity is concentrated at sites of PMN accumulation, i.e. sites of infection and/or inflammation. This is the first study to analyse the accuracy of the procedure in the differential diagnosis of suspected intraperitoneal sepsis in patients following gastrointestinal surgery. Sixty-six scans were performed in 43 patients: 43 scans were negative; 37 of these proved to be clinically negative and represent true negative scans. The remaining 6 (9 per cent) scans proved to be false negative, i.e. the patients in fact had infection. Twenty-three scans were positive; 19 were truly positive, 2 (6 per cent) were false positives and 2 (6 per cent) were equivocal (representing clinical inflammation but no infection). Thus the overall accuracy of this non-invasive, relatively rapid diagnostic procedure was 85 per cent. This is certainly the single most accurate readily adaptable technique in the diagnosis and localization of covert sepsis in the surgical patient.

6. The release of vasoactive intestinal peptide during altered mid-gut blood flow

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(*see* Volume 67, January 1980)

7. Serum prolactin levels in the Zollinger–Ellison syndrome

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Human serum prolactin (PRL) levels were measured in 37 patients with proved Zollinger–Ellison syndrome (ZES). Eight patients had elevated levels (>12 μg/l in males and >21 μg/l in females). There was no correlation between serum PRL levels and serum gastrin levels, gastrinoma mass, or serum HCG levels.

Five of these eight patients had other evidence of MEA. In the remaining 3 patients, an MEA syndrome was evidenced only by the elevated PRL level. One of the 5 patients with obvious MEA developed visual field defects and radiographic evidence of sella turcica erosion. This was the only patient with an elevated PRL level (43 μg/l) known to have developed a demonstrable pituitary tumour. Studies over 4–5 years in 3 patients showed a tendency for serum PRL levels to increase modestly.

An elevated serum PRL level is a frequent finding in patients with ZES. While it is found most often in patients with obvious MEA syndromes, a number of patients may have high PRL levels without other evidence supporting multiglandular disease. Since levels tend to increase with time, and clinically significant pituitary tumours can develop, it is recommended that all patients with ZES have serial serum PRL determinations performed.

8. Are gastric prostaglandins regulators of gastric acid secretion?

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We have previously demonstrated that at a constant rate of infusion of pentagastrin, histamine and insulin there are similar positive correlations between outputs of acid and immunoreactive PGE into gastric juice. To test the hypothesis that PFE may be involved in a local negative feedback mechanism for the control of acid secretion this relationship has been further studied in six conscious cats with gastric fistulas following incremental doses of pentagastrin (1–32 $\mu g\ kg^{-1}\ h^{-1}$)

and histamine (50–375 μg kg^{-1} h^{-1}) with and without flurbiprofen, a prostaglandin synthesis inhibitor. There was a significant linear acid secretory response to incremental doses of both pentagastrin and histamine ($r = 0{\cdot}981$, $P = 0{\cdot}018$); however, in neither experiment was the output of PGE (measured by radioimmunoassay) dose-dependent. Following a predose (0·2 mg/kg) and the simultaneous infusion of flurbiprofen (0·1 mg kg^{-1} h^{-1}), the acid secretory response to pentagastrin and histamine remained unchanged despite inhibition of gastric PGE output (>60 per cent).

Pentagastrin (μg kg^{-1} h^{-1})	[illegible]	2	4	8	16	32
PGE output pg kg^{-1} 15 min^{-1}						
	87	366	214	105	93	176
	±49	±60	±34	±19	±10	±26
Acid output μmmol kg^{-1} 15 min^{-1}						
	234	303	383	375	415	417
	±28	±23	±30	±36	±35	±29
Acid output after flurbiprofen μmol kg^{-1} 15 min^{-1}						
	239	300	367	402	368	367
	±34	±44	±51	±46	±35	±25

Histamine (μg kg^{-1} h^{-1})	50	125	250	375
PGE output pg kg^{-1} 15 min^{-1}				
	73	68	178	144
	±15	±12	±25	±36
Acid output μmmol kg^{-1} 15 min^{-1}				
	140	308	393	410
	±25	±34	±33	±46
Acid output after flurbiprofen μmol kg^{-1} 15 min^{-1}				
	168	320	417	443
	±32	±33	±35	±42

The failure of PGE to correlate with acid output in dose-response experiments and the lack of potentiation of acid secretion during inhibition of endogenous prostaglandin synthesis suggests that the proposed negative feedback mechanism involving PGE in gastric juice is incorrect.

9. Calcium infusion—a new provocative test for insulinomas

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The differentiation of insulin-secreting tumours of the pancreas from other hypoglycaemic states is often difficult and time-consuming. Calcium infusion has been used in the diagnosis of gastrinomas, medullary carcinomas of the thyroid and carcinoid syndromes. The purpose of this paper is to report that this infusion is also useful in the preoperative diagnosis of insulinomas.

Thirteen patients with hypoglycaemia were evaluated by standard techniques—prolonged fasting, i.v. tolbutamide and oral glucose tolerance tests. In addition, each of these patients and 5 normoglycaemic volunteers received an infusion of calcium gluconate, 10 mg Ca^{++}/kg in saline over a 2-hour period. Peripheral blood which was drawn before and during these infusions was analysed for serum glucose, immunoreactive insulin and calcium concentrations. Eight of the hypoglycaemic patients were found at operation to have benign or malignant islet cell tumours of the pancreas; one child had islet cell hyperplasia and 4 patients were diagnosed as having reactive hypoglycaemia and were not operated upon.

In each of 8 patients with a confirmed islet-cell tumour, blood glucose values decreased within 60–90 min of the start of calcium infusion, necessitating the discontinuation of the infusion because of hypoglycaemic symptoms in most patients. Serum insulin values became clearly elevated above basal values in 6 of 8 patients. The serum glucose to insulin ratio decreased on all 8 patients. Postoperatively, calcium infusion was repeated in 5 patients in whom insulinomas had been removed. At this time no change in serum glucose or insulin levels occurred.

In contrast to the above individuals, in one patient with proved islet cell hyperplasia, in 4 patients with reactive hypoglycaemia and 5 in normoglycaemic volunteers, calcium infusion resulted in no changes in circulating glucose or insulin.

It is concluded that calcium infusion is a safe, rapid and effective provocative test which aids the preoperative diagnosis of benign or malignant insulin-secreting tumours of the pancreas.

10. The relationship between peptic ulcer localization and gastric acid secretion, gastric emptying and gastric secretion

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It is generally accepted that there is a close relationship between the prepyloric gastric ulcer and the duodenal ulcer. However, the results of HSV in patients with a prepyloric ulcer are not encouraging. Therefore it is suggested that the underlying pathophysiologic mechanism is different from that producing duodenal ulcer.

Three groups with different localization of peptic ulcer were investigated:

Group I: Acute duodenal ulcer (DU) ($n = 36$; male 31, female 5; age: 37·5 yr (27–72)).
Group II: Prepyloric ulcer (PPU) ($n = 6$; male 4, female 2; age: 44 yr (32–57)).
Group III: High gastric ulcer (HGU) ($n = 10$; male 4, female 6; age: 60 yr (37–86)).

The following tests were performed: gastric acid output; gastric emptying and serum gastrin level before and after the ingestion of a semi-solid meal. For statistical analysis the Mann–Whitney U test was used.

BAO, MAO and PAO of the patients with DU are significantly higher than in the patients with a HGU ($P < 0{\cdot}001$). Patients with a PPU have a significantly higher PAO than the patients with a HGU ($P < 0{\cdot}05$) and show lower values compared to DU patients ($P < 0{\cdot}1$). The $T_{\frac{1}{2}}$ of the DU patients is 21 min shorter than the $T_{\frac{1}{2}}$ of the HGU patients ($P < 0{\cdot}1$). The PPU patients have again an intermediate position. In contrast to these results the gastrin levels of DU and HGU patients are nearly identical and both are much lower than in the PPU patients.

Patients with a prepyloric ulcer have a lower acid output and a longer $T_{\frac{1}{2}}$ than the patients with duodenal ulcer. However, most surprising is that the gastrin levels are nearly two-fold higher. These results suggest that the therapeutic approach in patients with a prepyloric ulcer may need reconsideration.

	Acid output (mmol/h)		
	BAO	MAO	PAO
DU ($n = 36$)	5·6 (0·6–18·5)	32·4 (14–52)	38 (15–67)
PPU ($n = 6$)	4·6 (0·5–7·2)	25·1 (7–39)	31 (8–45)
HGU ($n = 10$)	2·6 (0 14–8·8)	19·8 (3·7–24)	21 (6–31)

	Serum gastrin (ng/l)		Gastrin emptying (min)
	G_{basal}	G_{peak}	$T_{\frac{1}{2}}$
Control	42 (25–84)	110 (35–138)	59 (38–77)
DU ($n \doteq 36$)	52·5 (18–238)	110 (55–450)	46 (21–154)
PPU ($n = 6$)	82 (22–140)	201 (39–516)	50 (33–123)
HGU ($n = 10$)	57 (35–132)	98 (87–266)	67 (31–127)

Median levels and range.

11. Amino acids as possible mediators of the intestinal phase of gastric secretion

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The recent demonstration that intravenous administration of a solution of L-amino acids (AA) evokes a gastric secretory response in dogs (Landor and Ipapo, 1977) and in man (Isenberg and Maxwell, 1978) has lent support to the idea that absorbed products of protein digestion account in part for the intestinal phase of gastric secretion In order to evaluate this possibility we measured Heidenhain pouch secretion and plasma amino nitrogen (PAN) in dogs subjected to 2-hour infusions of AA given via different routes. In 6 dogs, 4 infusions into the portal venous system and 4 infusions into the jejunum were carried out; in 4 dogs with portacaval transposition, 4 infusions into peripheral veins and 4 infusions into the jejunum were done.

In the first group of dogs, in which AA were infused into, or absorbed into, the portal circulation, mean secretion was 4·6 per cent of the maximal histamine response (MHR) after portal infusion and 3·9 per cent MHR after intrajejunal infusion ($P>0\ 6$); comparable figures for PAN were 5·3 mg/100 ml and 5·8 mg/100 ml ($P>0{\cdot}6$). Among the dogs in which AA was infused into, or absorbed into, the peripheral circulation, mean secretion was 21 per cent MHR after i.v. AA and 19·4 per cent MHR after intrajejunal AA ($P>0{\cdot}36$); PAN was 7·5 mg/100 ml and 6·4 mg/100 ml respectively ($P>0{\cdot}13$). Thus, in these two differing circumstances, gastric secretion and PAN were comparably elevated by infusion of AA into the venous circulation or into the gut. The data support the contention that absorbed amino acids account for a substantial portion, if not all, of the intestinal phase of secretion.

ISENBERG J. I. and MAXWELL V. (1978) Intravenous infusion of amino acid stimulates gastric acid secretion in man. *N. Engl. J. Med.* **298**, 27–29.

LANDOR J. H. and IPAPO V. S. (1977) Gastric secretory effect of amino acids given enterally and parenterally in dogs. *Gastroenterology* **73**, 781–784.

12. Endogenous immunosuppression, plasma inhibitors and the outcome of renal transplantation

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Evidence now suggests that the residual cell-mediated immunity of the regular dialysis treatment (RDT) patients, as tested with dinitrochlorobenzene (DNCB), plays a role in the outcome of renal transplantation (Rolley et al., 1977; Diamondopoulos et al., 1978). In this study the results of quantitative DNCB testing and the outcome of transplantation in 47 first cadaver kidney transplants is reported and the analysis of serum factors blocking lymphocyte response to the mitogens PHA, PWM and Con A. Mitogen responses are given as the stimulation index in control plasma or in the patients' own (autologous) plasma.

	DNCB score 0–3	 3+	*P*
6 m graft Survival	71%	17%	
Control plasma			
PHA	67±16	148±54	n.s.
PWM	32±10	86±26	$P<0{\cdot}05$
Con A	19±7·5	43±10·1	$P<0{\cdot}05$
Autologous plasma			
PHA	61±21	128±65	n.s.
PWM	30±12	92±33	n.s.
Con A	13·7±5·7	43±11·9	$P<0{\cdot}05$

These results show that the good graft outcome in RDT patients with a low DNCB response is associated with a depression of mitogen response of the lymphocytes from the low DNCB responders. This depression was seen in control plasma; autologous plasma gave an additional small depression of the response. It is concluded that the failure of RDT patients to respond to DNCB is associated with depressed lymphocyte function, and serum factors play a lesser role.

ROLLEY R., STERIOFF S., PARKS L. et al. (1977) Delayed cutaneous hypersensitivity and human renal allotransplantation. *Transplantation Proc.* **9**, 81–83.

DIAMONDOPOULOS A. A., HAMILTON D. N. H. and BRIGGS J. D. (1977) A new predictive factor for the outcome of renal transplantation. *Dial. Transplant. Nephrol.* **15**, 233–288.

13. Transplantation tolerance following total lymphoid irradiation [TLI] and allogeneic bone marrow (BM) injection in primates

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Tolerance to allogeneic skin and heart grafts and stable chimerism can be established in rodents by TLI and allogeneic BM injection (Slavin et al., 1978). The application of this concept has been studied in liver allotransplantation in two groups of outbred Chacma baboons. Group 1 (6 baboons) received 800 rad to the thorax and abdomen in two fractions 24 h apart, with shielding of the lungs and iliac crests. Five baboons received 6 3–40·4 × 10^7 nucleated BM cells per kg after the second fraction of irradiation, followed immediately by an orthotopic liver allograft from the BM donor. Four animals died 7, 8, 9 and 9 days after transplantation from massive intraperitoneal haemorrhage. All were profoundly thrombocytopenic on day 6. Histology of the liver at autopsy showed minimal or no evidence of cellular rejection. One baboon survived for 47 days (median survival of untreated controls, 19 days). The sixth animal received donor BM and a liver allograft 79 days after TLI, and is alive 32 days after transplantation. Group 2 (4 baboons) received eight 200 rad fractions to the torso without lung shielding in 15 days, followed immediately by allogeneic donor BM (4·4–13·6 × 10^7/kg). Orthotopic liver transplantation from the BM donors was carried out 15–23 days later. All animals are alive 46–54 days after transplantation. Two baboons have had normal serum bilirubin values throughout, and may be fully tolerant. BM chimerism has been documented in 2 animals, without any clinical evidence of graft versus host disease. Two baboons have developed anti-donor B cell antibodies after transplantation. Cell mediated lympholysis has been persistently negative in all animals and their T cells have remained unresponsive to phytohaemagglutinin.

SLAVIN S., REITZ B., BIEBER C. P. et al. (1978) Transplantation tolerance in adult rats using total lymphoid irradiation. *J. Exp. Med.* **147**, 700–707.

14. Ia (DRw) antigen expression on human kidney and other tissues

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It has been shown recently that renal transplantation can be performed successfully in the presence of donor-specific sensitization as shown by a positive crossmatch (previously considered an absolute contraindication to transplantation) where the antibody in the recipient is directed against B lymphocyte antigens. These antibodies against donor B lymphocytes have been considered to be directed in part against HLA-DRw antigens, analogous to the Ia antigens in the mouse. These antigens were thought to have a limited tissue distribution, being expressed on B lymphocytes and macrophages, but not on renal tissue in particular. This has been considered an explanation for the success of a renal transplant performed in the presence of this type of positive crossmatch. Recent animal studies, however, have demonstrated the presence of Ia antigens in substantial amounts on a wider range of tissues, including kidney in both rat and guinea-pig.

Two monoclonal antibodies against HLA-DRw and HLA-ABC were produced by hybridomas formed from a mouse myeloma/mouse spleen cell fusion, following hyperimmunization of the spleen cell donors with membranes from a lymphoblastoid B cell line and tonsil leucocytes, respectively. These antibodies were absorbed quantitatively with ten different human tissues and assayed in an indirect binding radioimmunoassay. Three separate normal kidney homogenates absorbed the anti-Ia activity as strongly as spleen (which carries a large amount of Ia antigen because of its large population of B lymphocytes). Liver and heart were tenfold and thirtyfold less effective by absorption. Ia was also detected in quantity on chronic lymphatic leukaemic cells, in marginal mounts on brain, on a small population of thymocytes and not at all on erythrocytes, platelets or reticulocytes. The distribution of HLA-ABC was widespread, as expected.

We conclude that human Ia antigens are expressed in different amounts on the commonly transplanted organs, kidney, liver and heart. Previous hypotheses of graft rejection and its suppression based on the absence of Ia antigens on human kidney are no longer acceptable.

15. Survival rates of immediately vascularized skin allografts

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A model for immediate vascularization of skin was devised to examine one explanation of the differential survival rates of freely grafted skin and organs, i.e. the increased vulnerability of skin to early ischaemic necrosis. Fischer (F) rat skin was transplanted beneath the kidney capsule of tolerant Lewis (L) recipients. This skin healed in normally and, after 30 days, the skin-kidney grafts were excised and immediately revascularized by microvascular techniques in normal L recipients (syngeneic to the kidney portion of the graft, allogeneic to the skin). For 5 days after transplantation of the composite graft, the skin appeared normal in 11 recipients. From 6 to 11 days, in 6 rats, an active inflammatory response developed at the skin–kidney interface. In 10 rats, after 12–21 days, rejection of the skin was complete. The renal portion of all composite grafts appeared normal and all recipients of composite grafts rejected orthotopic F skin in an accelerated manner (median survival times: 8·2 *v.* 11·5 days in F→L controls), demonstrating that the skin on the composite graft had retained its antigenicity. These results demonstrate that immediately vascularized skin allografts will still be rejected within 2 weeks compared to survivals of up to 48 weeks for renal allografts across the same histocompatibility barrier. Anatomical factors are not sufficient to account for the differences in survival times between skin and solid organs.

16. Studies of the action of cyclosporin A on rabbit renal allografts

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We have used Cyclosporin A (Cy A) in over 80 renal allografted nephrectomized rabbits and shown that grafts can remain in excellent condition for as long as 257 days on continuous treatment. Early rejection has not followed cessation of treatment after 28 days or 18 days. It has been suggested that such courses of Cy A treatment, given with an antigenic challenge, can result in permanent specific allograft acceptance, by destroying the clones of lymphocytes reacting to that antigen. However, in our experience this post treatment 'tolerance' is not in fact wholly specific as we have shown that second kidneys taken from a third party donor can be accepted during this period.

We now present the results of giving Cy A (25 mg kg^{-1} d^{-1} i.m.) for (*a*) 14 days only after grafting and (*b*) for 14 days stopping 7 days before grafting.

Results: (*a*) Eleven rabbits treated after grafting have a mean survival so far of over 40 days (untreated: mean = 11 days, $P<0\cdot001$). Five are still alive and 3 have so far accepted their allografts for 3 months. Two delayed rejections have occurred at 44 and 54 days.

(*b*) Five rabbits grafted 1 week after treatment ceased have a mean survival of over 26 days so far ($P<0\cdot01$). Three are still alive at up to 45 days. Two died of tubular necrosis at 5 and 13 days with no significant rejection on histology.

These results show that 14 days' Cy A therapy is sufficient to induce the long term allograft acceptance state. However, we have seen delayed rejection in this group, even when therapy was continued as long as 56 days. No such rejection has yet been seen in rabbits given continuous therapy.

The unexpected and unique finding that prior treatment alone is immunosuppressive indicates that Cy A persists in the recipient and this must be taken into account in understanding post-Cy A 'tolerance'.

Overall our results favour a prolonged and not wholly specific effect of Cy A treatment which may wear off very slowly. They do not lend support to a theory of permanent specific clonal deletion by the drug.

17. Transfusions of whole blood, leucocytes and erythrocytes and renal allograft survival in DLA-typed beagles

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Blood transfusions have a protective effect on a subsequent kidney allograft in man. However, the optimal transfusion policy of patients with an end-stage renal failure is not known. Besides the beneficial effects, blood transfusions carry the risk of inducing lymphocytotoxic allograft antibodies that can exclude potential recipients from kidney transplantation or have a deleterious effect on the graft. Experiments have been carried out to study the effect of blood transfusions on renal allograft survival in some 80 DLA-typed beagles. Pretreatment with kidney blood donor (i.v. or s.c.) did not prolong graft survival but led to positive cross-match tests and accelerated graft rejection in the pretreated dogs. Transfusions with pooled third party blood before transplantation induced a broad spectrum of antibodies and did not give rise to graft protection although no accelerated graft rejection was seen. Immune response against a random panel was not genetically determined and did not correlate with graft rejection. Transfusions of (non-pooled) third party blood and postoperative immunosuppression led to absence of graft rejection in 6 out of 10 transfused beagles, whereas of 9 non-transfused control littermates only one was a long term survivor. To determine which fragment of the whole blood was responsible for the protection of the future allograft, 12 DLA-typed beagles were transfused with three erythrocyte suspensions (ERY) of different non-related donors and 12 littermates were transfused with three leucocyte suspensions (LEU) of the same donors. Two weeks after the last transfusions kidneys from non-related mongrel donors were grafted to both erythrocyte and leucocyte pretreated beagle littermate recipients. Immunosuppressive treatment was given postoperatively (Imuran 2 mg/kg, prednisolone 1 mg/kg i.v.). Immunoresponsiveness was measured before transplantation. The survival times are given below and can be compared with similar data of whole blood (WB) and non-tranfused (NTR) dogs.

ERY: 5+, 7+, 9, 16+, 24, 47, 51, >60+, >60+.
LEU: 4+, 6+, 8, 12, 32, >60, >60, >60, >60.
WB: 21, 26, 51, >60, >60, >60, >60, >60, >60.
NTR: 11, 15, 16, 19, 20, 29, 30, 48, >60.

+ = Positive cross-match before transplantation between kidney donor and recipient.

It is concluded that (*a*) specific immune response could not be measured in the beagle recipients; (*b*) protective effect on renal allograft pretreatment with third party blood transfusions was only apparent when immunosuppression was given postoperatively; (3) the protective effect could not solely be contributed to the erythrocytes or leucocytes.

18. Postoperative pulmonary dysfunction: the role of intravascular platelet aggregates

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Postoperative hypoxia, a common clinical problem, is widely thought to result primarily from respiratory suppression due to anaesthesia and wound pain. However, in trauma patients attention has recently focused upon the possible role of intravascular platelet aggregates (IPA) in pulmonary damage following shock (Moseley and Doty, 1970). IPA may now be measured reproducibly by a modified screen filter technique and can be demonstrated in patients after major surgery (McCollum, 1978). In this study we investigated the relationship between IPA levels and postoperative dysfunction.

In 20 patients, IPA levels were measured by screen filtration of femoral vein blood 30 min and 3 h following surgery. Pulmonary function (arterial Po_2, physiological dead space and alveolar/arterial Po_2 gradient) was estimated preoperatively and on days 1 and 7 postoperatively. A significant relationship was noted between these IPA levels and subsequent measurement of pulmonary function. In patients with elevated IPA levels the mean fall in arterial Po_2 was greater at 7 days (1·8 kPa, 13·5 mmHg) than in patients with normal IPA levels (0·7 kPa, 5·4 mmHg) ($P<0·05$). This was explained by a marked increase in alveolar/arterial Po_2 gradient in these patients (2·2 kPa, 16·5 mmHg *v.* 0·5 kPa, 3.6 mmHg) ($P<0·01$). The postoperative fall in platelet count was the only other parameter which was related to pulmonary dysfunction on day 7.

These results indicate that elevated IPA levels immediately after surgery predict pulmonary dysfunction 1 week later. Therapeutic manoeuvres to prevent IPA may conceivably reduce postoperative hypoxia.

MCCOLLUM C. N. (1978) Intravascular platelet aggregation: can it be measured in surgical patients, and does it matter? *Br. J. Surg.* 65, 813.

MOSELEY R. V. and DOTY D. B. (1970) Death associated with multiple pulmonary emboli after battle injury. *Ann. Surg.* 171, 336–346.

19. Effects of burn injury and sepsis on visceral blood flow

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Most of the increase in cardiac output in thermally injured patients is directed to the burn wound, but flow to visceral tissues remains poorly defined. In this study, visceral circulation and oxygen uptake were determined by measuring splanchnic blood flow (ICG extraction), renal blood flow (PAH clearance), cardiac index (dye dilution), total body oxygen consumption and regional oxygen extraction (A-Vo_2 by selective venous catheterization) in 9 uninjured controls and in 19 non-infected burn patients (mean burn size 47 per cent TBS) studied 7–21 days after injury. To assess the added impact of sepsis, 10 normotensive, bacteraemic burn patients (59·5 per cent TBS) were also studied. Results are expressed as mean±s.e. mean, flow in $1\ \text{min}^{-1}\ \text{m}^{-2}$, and A-Vo_2 in ml/100 ml blood.

	Total body		Splanchnic	
	Flow*	A-Vo_2	Flow	A-Vo_2
Normals	3·43	3·73	0 74†	4·5†
	±0 22	±0·12		
Non-infected	7·80	3·33	1·38	4·80
	±0·42	±0·58	±0·10	±0·29
Bacteraemic**	8·52	2·86	1·78	3·94
	±0·35	±0·17	±0·19	±0·52

	Renal	
	Flow	A-Vo_2
Normals	0·55	1·70†
	±0·04	
Non-infected	0·81	2·10
	±0·08	±0·12
Bacteraemic**	1·97‡	0·98
	±0·38	±0·19

* Cardiac index; † From literature; ‡ $n=3$, assumed PAH extraction ratio = 0·46†.

** Only significant differences between patient groups were in renal values, $P<0·001$.

Both splanchnic and renal flow are increased as a direct consequence of injury. The elevated visceral blood flow in non-septic patients appears appropriate for heightened metabolic demands, since regional A-Vo_2 differences remain essentially normal. The added insult of sepsis did not significantly alter total body and splanchnic blood flow but appeared to increase renal perfusion in excess of aerobic requirements.

20. Role of the carotid sinus reflex as a possible mechanism of the effect of intra-aortic balloon pumping for the treatment of shock

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Intra-aortic balloon pumping (IABP) is now widely used as an effective adjunct to medical and surgical therapy of either cardiogenic shock secondary to acute myocardial infarction or post-surgical acute heart failure, or the inability to wean from cardiopulmonary bypass.

The mechanisms of the effect of IABP have been explained by the following: (*a*) augmentation of the coronary artery blood flow during ventricular diastole; (*b*) unloading of left ventricular afterload during systole resulting in a decrease in the left ventricular end-diastolic pressure due to the mechanical balloon counterpulsation in the descending thoracic aorta.

In this report the predictive value of the carotid sinus baroreceptor response to the diastolic IABP is described as another possible mechanism to explain the improvement of cardiocirculatory dynamics following the IABP.

In the mongrel dog, firing impulses were introduced and recorded from the carotid sinus nerve during IABP. ECG, carotid pressure, flow and venous pressure were monitored.

The burst of impulses was initiated by the diastolic rise in the carotid pressure during IABP, less impulses being observed during systole and even less during diastole.

During the cardiac cycle with IABP the average activity of the carotid sinus nerve was 70 000 µV/ms whereas during the cardiac cycle without IABP the average activity was 52 000 µV/ms.

With increase in blood pressure in the carotid, the frequency of firing of the sinus nerve is enhanced. An increase in firing, as occurred in the phase of diastole with IABP, might act to inhibit the vasoconstrictor centre by a reflex mechanism resulting in peripheral vasodilatation and lowering the systemic vascular resistance in shock state.

The role of the carotid sinus reflex is a possible mechanism for the effect of IABP.

21. The hepatic handling of bromsulphthalein (BSP) following graded haemorrhage

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Hepatic decompensation is well recognized following major surgery or trauma. An important contributing factor is blood loss, but it is not known whether the magnitude of the change in hepatic function correlates with the severity of the blood loss. In this study, the hepatic handling of BSP has been measured in pigs following mild, moderate and severe haemorrhage (10 per cent, 20 per cent and 30 per cent of calculated blood volume).

The experiments were performed in anaesthetized animals 3 days after the placement of sampling catheters in the hepatic inflow and outflow vessels, and the construction of an external bile shunt. BSP was infused at a rate of 0·59 $\mu\text{mol kg}^{-1}\ \text{min}^{-1}$ and bile flow, BSP concentration in serum and bile, and BSP conjugates in bile were measured for 6 h after the bleed.

There was a significant reduction in the proportion of BSP conjugates in bile, and there was a significant positive correlation between the degree of this reduction and the degree of blood loss.

The mechanism of this reduced biliary excretion of BSP conjugates may be the result of impairment of BSP conjugation or inhibition of biliary excretion of conjugates or both.

22. Studies on the plasma kallikrein-kinin system during experimentally induced endotoxaemia in dogs and septicaemia in man

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Various studies over the past decade have suggested that the plasma kallikrein-kinin system becomes activated during experimentally induced endotoxaemia in animals and septicaemia in man. Using a large number of tests including newly developed assays with chromogenic peptide substrates, we have studied various components of the plasma kallikrein-kinin system in endotoxaemia in a dog model and in plasma samples from normal subjects and patients with septicaemia. Endotoxin shock was induced in Labrador retriever dogs by infusing a lethal dose (6 mg/kg) of *E. coli* endotoxin over a 3 hour period. Plasma levels of prekallikrein (PKK), kallikrein (KK) and kallikrein inhibitors (KKI) were monitored during and after the infusion, using a chromogenic peptide substrate for plasma KK (Chromozyme-PK, Pentapharm, Basle, Switzerland). High molecular weight kininogen (HMwK) levels were determined by incubating plasma samples with purified human plasma kallikrein and determining the bradykinin liberated on the isolated rat uterus. Considerable reductions in plasma levels of PKK and HMwK were seen in the collapse samples and free KK and KK bound to α_2-macroglobulin (α_2M) were detected. Functional KK inhibition (KKI) was also reduced.

Levels of Hageman factor (HF), KK, PKK, HMwK, KKI and concentrations of C^1-esterase inhibitor (CIINH, the major protease inhibitor in the plasma KK-kinin system), α_2M and α_1-antitrypsin (α_1AT) were determined in plasma samples from normal individuals and patients with septicaemia. Considerably lower levels of HF, PKK and HMwK and lower levels of KKI and α_2M were found in patients with septicaemia of fatal outcome. Spontaneous KK activity was higher and markedly increased concentrations of CIINH and α_1AT were also found. Our results emphasize that the plasma KK-kinin system becomes activated during experimentally induced endotoxaemia in dogs and septicaemia in man and suggest that the resulting release of bradykinin contributes to the development of shock in this state. During both endotoxaemia and septicaemia, consumption of components of the system (HF, PKK and HMwK) occurs, plasma KK activity can be detected in the plasma and functional kallikrein inhibition is markedly reduced. Because mean plasma levels of PKK, HMwK and CIINH were higher in 3 patients with septicaemia who subsequently recovered, and functional KKI was normal, it is probable that functional kallikrein inhibition of active proteases in septicaemia contributes to survival.

23. The metabolism of biogenic amines during septic shock

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It is the purpose of this investigation to determine the effect of *E. coli* induced shock on the capacity of the lung to extract two biogenic amines, adrenaline (A) and 5-hydroxytryptamine (5-HT). Four adult male baboons were anaesthetized, intubated and ventilated. Sepsis was induced by a continuous 4-h intravenous infusion of live *E. coli*. Blood gases and central haemodynamic pressures were serially recorded. Simultaneous indicator dilution curves were generated using ^{14}C-labelled 5-HT and ^{3}H-labelled A. The labels were injected into a central vein and collected from an aortic catheter.

The increased recovery of 5-HT following septic shock may be explained by (*a*) increased arteriovenous pulmonary shunting, (*b*) capillary endothelial damage or (*c*) interstitial pulmonary oedema inhibiting pulmonary metabolism.

It is concluded that septic shock reduces pulmonary extraction of 5-HT in the baboon. These data suggest that pulmonary endothelial metabolism is significantly altered during acute sepsis.

Table I: RECOVERY OF A AND 5-HT

	Percent recovery		
	Before sepsis	After sepsis	
A	100%	100%	n.s.
5-HT	32·8±3·6%	42·5±4·9%	$P<0·05$

Table II: MEAN ARTERIAL AND PULMONARY WEDGE PRESSURE

	Before sepsis	After sepsis	
MAP	121·3±9·6 mmHg	58·8±15·4 mmHg	$P<0·05$
PAWP	13·0±1·5 mmHg	21·3±4·9 mmHg	n.s.
Qs/Qt	0·07±0·05	0·33±0·09	$P<0·05$

All results: mean±s.e. mean.

24. A single fibre electromyographic study of the external anal sphincter in normal subjects, rectal prolapse and in anorectal incontinence

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In the past, investigation of patients with anorectal incontinence has relied on anal pressure studies, supported by electromyography and, more recently, by study of the anal reflex (Henry and Swash, 1978). Parks et al. (1977) reported histological abnormalities in the anal musculature, and suggested that the innervation of the external sphincter (EAS) and puborectalis muscles was damaged in these patients.

In order to study the functional disorder in the EAS, we have utilized the single fibre technique devised by Stålberg and Ekstedt (1973). This technique gives a quantitative measure of the mean number of muscle fibres supplied by a motor unit within the uptake radius of the electrode tip: the fibre density (FD). In 13 normal subjects aged 20–80 years the mean FD was 1·5 (s.d. 0·2). In 14 patients with idiopathic anorectal incontinence with delayed anal reflex latency, the mean FD in the EAS was 2·14 (s.d. 0·28) ($P\pm0·001$). In 10 patients with rectal prolapse without incontinence the mean FD was 1·9 (s.d. 0·27) ($P<0·01$).

These results suggest that the pattern of innervation of the EAS has become reorganized in idiopathic anorectal incontinence and is consistent with histological abnormalities described.

Single fibre electromyography may be useful in the assessment of patients with anorectal disorders since an increase in FD may be a predictor of future incontinence.

HENRY M. M. and SWASH M. (1978) Assessment of pelvic floor disorders and incontinence by electrophysiological recording of the anal reflex. *Lancet* 1, 1290–1291.

PARKS A. G., SWASH M. and URICH H. (1977) Sphincter denervation in anorectal incontinence and rectal prolapse. *Gut* 18, 656–665.

STÅLBERG E. and EKSTEDT A. (1973) Single fibre emg and microphysiology of the motor unit in normal and diseased human muscle. In: DESMEDT J. E. (ed.) *New Developments in Electromyography and Clinical Neurophysiology.* Basle, Karger, vol. 1, pp. 89–112.

25. Intestinal motility and acute alcohol ingestion: electromyographic studies in dogs

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The fasting state in dogs is characterized by a cyclic phenomenon, the myoelectric complex (MC). The most characteristic phase of the MC is phase III that recurs about every 90 min. The aim of this work is to study the effects of acute alcohol ingestion on MC recurrence.

Two groups of 5 dogs are prepared with a duodenal cannula allowing direct intraduodenal administration (IDA) of alcohol. Electrodes implanted on jejunal serosa allow chronic recordings of intestinal myoelectrical activity. In each dog of group one the effects of alcohol IDA are studied with solutions of three concentrations (4 per cent, 6 per cent and 8 per cent v/v). In each dog of group two, IDA of the 4 per cent alcohol solution is tested and blood alcohol concentration (BAC) is studied every 20 min after the beginning of IDA. In each experiment the solution administered (volume of 300 ml) takes 30 min to perfuse.

In group one, taking each dog as its own reference, a significant recurrence delay in phase III of 30±15 min, 60±15 min and 100±25 min is observed after IDA of solutions respectively of 4 per cent, 6 per cent and 8 per cent alcohol. In group two, the curves of BAC versus time show a phase of fast increasing BAC followed by a phase of slow decreasing BAC. The peak value of the curve occurring at 85±15 min after IDA beginning in all dogs is significantly different in each dog.

The recurrence of phase III is observed 120±15 min after beginning of IDA when BAC decreases.

We conclude that: (*a*) alcohol at a concentration over 4 per cent induces a delay of MC recurrence related to the dose administered; (*b*) for the same alcohol concentration reappearance of phase III of the MC is independent of maximal BAC and occurs after maximal alcohol absorption rate is reached. This suggests that alcohol acts very rapidly on intestinal motility.

26. Evidence for the flutter valve mechanism of the lower oesophageal high pressure zone (HPZ)

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As the HPZ pressure does not adequately reflect competence at the cardio-oesophageal junction (Clark et al., 1976), a study was undertaken to assess the force exerted by the HPZ and its intra-abdominal segment in relation to reflux control. Simultaneous manometry, HPZ length and oesophageal pH were recorded in 189 patients at rest and during raised intra-abdominal pressure produced by 50·0 mmHg abdominal cuff compression after the instillation of 300 ml 0·1 HCl in the stomach. The force in Newtons × 10^{-2} was calculated for 1·0 cm strips of both the entire length of the HPZ and its intra-abdominal segment (IAS) as follows: force = length (cm) × breadth (cm) × pressure (mmHg) × 1·33.

During abdominal compression, 102 patients refluxed as shown by a fall in the oesophageal pH to below 4 0.

The results obtained are shown in the following table:

	Force (N × 10^{-2} [$\bar{x}$, s.e. mean]) HPZ	
	Rest	Compression
Refluxers (n = 102)	63·2±4·0	*38·1±2·8
Non-refluxers (n = 87)	97·2±5·1	*63·3±3·5

	Force (N × 10^{-2} [$\bar{x}$, s.e. mean]) IAS	
	Rest	Compression
Refluxers (n = 102)	32·4±2·9	*16·8±1 7
Non-refluxers (n = 87)	59·1±3·5	*34·3±2·7

$P < 0·001$ rank sum.

The force ratio IAS/HPZ fell below 0·5 (0·44) only in the reflux group during abdominal compression indicating that increased intra-abdominal pressure in these patients causes a reversal of the force distribution of the HPZ on either side of the diaphragm.

It is concluded that the resting HPZ force, like the resting HPZ pressure, does not determine competence at the cardio-oesophageal junction which appears to depend on the reserve of force (and pressure) which ensures the persistence of a threshold barrier against reflux whenever intra-abdominal pressure is raised, and maintains a force differential along the HPZ in favour of the intra-abdominal segment. These findings suggest that the HPZ behaves like a flutter valve and argues against it being a physiological sphincter.

CLARK J., MOOSSA A. R. and SKINNER D. B. (1976) Pitfalls in the performance and interpretation of oesophageal function tests. *Surg. Clin. North Am.* **56**, 29–37.

27. The effect of experimental chemical uraemia on serum gastrin levels in dogs

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The hypergastrinaemia of renal failure is now well recognized (Falcao et al., 1975). Whether uraemia *per se*—in addition to the loss of functioning renal parenchyma—can produce hypergastrinaemia, however, is unclear (Davidson et al., 1974). This study was undertaken to clarify this question, as well as to clarify the effect of acute uraemia on BAO.

Five dogs underwent studies of BAO and arterial pH before and after bilateral nephrectomy. Acute uraemia was produced in two other groups of dogs by bilateral ureteral ligation or bilateral ureterovena caval diversion. The latter procedure produces the chemical changes of uraemia while leaving the kidneys structurally intact. Control and postoperative values of BUN, creatinine and serum gastrin were determined for all three groups.

The nephrectomized dogs showed a twentyfold increase in BAO during the postoperative period which was significantly greater than the average control value ($P < 0 001$). This acid hypersecretion was not associated with arterial acidosis. Marked hypergastrinaemia—to average levels as high as 422 ng/l—tended to parallel massive uraemia in all three experimental groups. Serum gastrin levels did not correlate with BAO.

Uraemia *per se*—not just the loss of renal parenchymal mass—plays a role in the genesis of uraemic hypergastrinaemia in dogs. In addition, factors other than—or in addition to—serum gastrin levels may be responsible for the gastric secretory response in uraemia.

DAVIDSON W. I., MOORE T. C., SHIPEY W. et al. (1974) Effect of bilateral nephrectomy and bilateral ureteral ligation on serum gastrin levels in the rat. *Gastroenterology* **66**, 522–525.

FALCAO H. A., WESDORP R. I. C. and FISCHER J. E. (1975) Gastrin levels and gastric acid secretion in anephric patients and in the patients with chronic and acute renal failure. *J. Surg. Res.* **18**, 107–111.

28. The importance of blood flow in the ability of gastric mucosa to maintain its intramural pH

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In spite of the presence of intraluminal bile salts and acid and its consequent back diffusion of H+, acute gastric ulcers do not occur unless ischaemia is also present. This observation suggests that, in the presence of normal mucosal blood flow (MBF), gastric mucosa is able to dispose of the influxing H+ and to prevent acidification and ulceration of the mucosa.

	Before ischaemia	
	Control	Test
MBF (ml min^{-1} g^{-1})	1·4±0·3	1·9±0·4
H^+ flux (μmol/min)	1·2±0·5	−6·1±0·8*
Intramural pH	7·2±0·1	7·2±0·2
Ulceration (%)	0/14 (0%)	0/14 (0%)

	During ischaemia	
	Control	Test
MBF (ml min^{-1} g^{-1})	0·2±0·1	0·3±0·2
H^+ flux (μmol/min)	1·8±0·6	−2·6±0·3*
Intramural pH	7·2±0·1	6·9±0·1*
Ulceration (%)	0/14 (0%)	13/14 (93%)*

Mean ± s.e. mean. *$P < 0·01$ when compared with control.

To evaluate this hypothesis, we determined the intramural pH of gastric mucosa using the microelectrode technique (Kivilaakso et al., 1978) in the presence of (*a*) back diffusion of H^+ and normal MBF, (*b*) back diffusion of H^+ and ischaemia and (*c*) ischaemia alone without back diffusion of H^+. In 19 dogs a portion of fundic stomach with intact vascular pedicle was placed in a single (n = 10) or a double (n = 9) lumen chamber. The control mucosae were bathed with acid solution (70 mmol HCl+80 mmol NaCl). Sodium taurocholate (5 mmol) was added to acid solution of test mucosae. After a normotensive period of 60 min, all mucosae were subjected to ischaemia induced by withdrawal of blood of 2 per cent of body weight for another 60 min. MBF was measured by gamma-labelled microspheres.

These results support the hypotheses that (*a*) adequate MBF (before ischaemia) disposes of influxing H^+ and maintains normal intramural pH and morphologic integrity of the mucosa even in the presence of back diffusion of H^+ and (*b*) ischaemia results in acidification and severe ulceration of the gastric mucosa as a consequence of compromised ability to dispose of H^+.

KIVILAAKSO E., FROMM D. and SILEN W. (1978) Relationship between ulceration and intramural pH of gastric mucosa during haemorrhagic shock. *Surgery* **84**, 70–78.

29. Is osmotic control of gastric emptying still present after vagotomy?

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Gastric emptying of liquid test meals is partly controlled by osmoreceptors situated in the duodenum. It has been reported that vagotomy abolishes this control (Hall and Read, 1970). In this study we have used the George technique to measure gastric emptying of 5 per cent and 10 per cent glucose test meals in 43 patients with duodenal ulcer, 17 patients with a recurrent ulcer and incomplete vagotomy and 35 patients who were symptomatic with an apparently complete vagotomy.

The results shown in the Table indicate that patients with a duodenal ulcer empty 10 per cent glucose meals significantly slower than 5 per cent glucose. It is also clear that regardless of the completeness of vagotomy the 10 per cent glucose test meal is emptied significantly slower than 5 per cent glucose in all postoperative patients, indicating a persistence of osmoregulatory control. Both postoperative groups of patients empty both types of test meal significantly faster than non-operated patients ($P<0{\cdot}01$).

Regrouping the postoperative patients irrespective of the completeness of vagotomy into 22 patients with a pyloroplasty and 30 patients with gastroenterostomy revealed that patients with a pyloroplasty did not retain significant differences in emptying of the two test meals whereas patients with a gastroenterostomy continued to empty the 10 per cent glucose significantly slower than the 5 per cent glucose.

These results suggest that osmoregulation of gastric emptying in the postoperative patient is not necessarily mediated by the vagus nerves and that the osmoreceptors are not confined to the duodenum.

Group	Indices	5% glucose	10% glucose
Duodenal ulcer	Starting index	5·0 min ± 2·4	19·3 min ± 2·5*
$n = 43$	Half-life	21·0 min ± 1·6	37·2 min ± 2·0*
	Emptying time	94·9 min ± 5·0	121·5 min ± 6·3*
Recurrent ulcer	Starting index	−15·2 min ± 5·5	−1·2 min ± 4·5*
(insulin positive)	Half-life	−0·7 min ± 4·3	14·2 min ± 4·9*
$n = 17$	Emptying time	65·5 min ± 11·0	84·7 min ± 11·9†
Symptomatic patients	Starting index	−15·1 min ± 4·7	−0·3 min ± 3·1*
(insulin negative)	Half-life	−0·2 min ± 3·4	15·7 min ± 2·8*
$n = 35$	Emptying time	62·7 min ± 8·0	81·0 min ± 8·8‡

Statistical analysis by the Wilcoxon test.
* $P<0{\cdot}01$. † N.s. ‡ $P<0{\cdot}05$.

HALL W. H. and READ R. C. (1970) Effect of vagotomy on gastric emptying time. *Am. J. Dig. Dis.* **15**, 1047–1053.

30. Multi-element analysis of the living body by neutron activation—a study of critically ill patients receiving intravenous nutrition (IVN)

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31. The postoperative insulin clearance of the human liver

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Animal experiments have shown that considerable amounts of insulin are removed by the liver. However, little information is available on hepatic insulin extraction in man.

In 10 non-diabetic surgical patients (5 M, 5 F) with normal liver function the hepatic insulin extraction rate was calculated by measuring simultaneously the insulin concentration in the portal and hepatic vein before, during and after i.v. glucose infusion ($1\ \mathrm{g\ kg\ BW}^{-1}\ 60\ \mathrm{min}^{-1}$). To demonstrate the enzymatic degradation of insulin by the human liver, insulin was incubated with the homogenates of 25 liver biopsies.

1. The hepatic insulin extraction rate ranges between 25 per cent (fasting state) and 60 per cent (after maximum glucose stimulation) of the portal venous insulin.
2. Up to a portal venous insulin concentration of about 400 U/l a linear correlation with the hepatic insulin extraction in man exists ($r = 0{\cdot}91$, $P<0{\cdot}0001$).
3. A soluble proteolytic hepatic enzyme which inactivates insulin was found in the $100\,000 \times g$ supernatant of human liver.
4. In fractionated liver homogenates, the $100\,000 \times g$ supernatant was found to be responsible for 88 per cent of the total hepatic insulin degrading activity in man. The V_{max} for insulin degradation was found to be $1{\cdot}75 \times 10^{-7}$ ($\simeq 68\ \mu g$ insulin/g liver).

The results demonstrate the important role of the human liver in the regulation of the postoperative insulin and glucose metabolism.

32. Influence of glucagon on plasma volume and osmolality during haemorrhagic shock

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Glucagon appears to improve some parameters of circulatory shock via a postulated positive inotropic effect. We have attempted to confirm this beneficial action and examine its mechanism. Rabbits, bled an amount equivalent to 25 per cent of their measured (^{131}I human serum albumin) blood volume were allowed to recover spontaneously during 90 min after which the shed blood was returned. Over the 90 min of hypovolaemic shock and the following 30 min of normovolaemic shock, we measured the following: arterial blood pressure (MABP), cardiac output (CO), superior mesenteric artery blood flow (SMABF), plasma volume (PV), arterial and venous haematocrits, glucose, lactate, Na, K and plasma osmolality. Thirty minutes after bleeding, the animals received a 30-min infusion of identical volumes of a solution of normal saline or of glucagon ($0{\cdot}04\ \mathrm{mg\ kg}^{-1}\ \mathrm{min}^{-1}$) or of xylose (0·6 mg/ml). Glucagon caused a marked improvement of CO and SMABF that lasted for at least 60 min after the infusion was over and that was mimicked by xylose. Animals receiving glucagon or xylose had a greater PV refill during shock than the controls. The greater repletion of PV was associated with and, we believe, caused by a greater rise in plasma osmolality. The latter was all accounted for in the case of the glucagon group by a marked enhancement of shock-induced hyperglycaemia. We suggest that glucagon increased the normal plasma refill during shock via a greater 'osmolar pull'. This, in conjunction with the lower total peripheral resistance brought about by a greater drop in haematocrit, suffices to explain the increases in CO and regional blood flow observed by others. According to this scheme, one would not expect glucagon to be effective in fasted animals or when prolonged shock has exhausted hepatic glycogen content. This may explain why some have not found glucagon to be beneficial.

33. Effect of epidural analgesia on postoperative sodium balance

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34. Isotope studies of substrate interaction in parenteral nutrition

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Total body nitrogen turnover, protein synthesis and breakdown have been measured in normal men given intravenous nutrients, using 15 N glycine as a tracer (Picou and Taylor-Roberts, 1969).

Sim et al. (1979) showed that changeover from oral diet to isonitrogenous amino acid infusion, lowered protein synthesis from 2·4±0·3 s.d. to 1·0±0·13 g $\mathrm{kg^{-1}\,d^{-1}}$ and breakdown from 2·4±0·3 to 1·8±0·2. Addition of 'high dose' glucose (about 500 g) to the amino acid infusion (AA+HDG) increased protein synthesis to 1·6±0·13 g $\mathrm{kg^{-1}\,d^{-1}}$, breakdown remaining unchanged.

This paper reports extended studies of substrate interaction. Subjects were given amino acids and fat emulsion (AA+FE, $n=4$) and amino acids, fat emulsion with 'low dose' glucose (150 g) (AA+FE+LDG, $n=4$), on isocaloric, isonitrogenous regimens of 5 days' duration.

Nitrogen turnover was the same in both groups.

Protein synthesis (2·0±0·2 g $\mathrm{kg^{-1}\,d^{-1}}$) was higher with AA+FE+LDG than with AA+FE (1·6±0·2, $P<0·02$), or with AA+HDG (1·6±0·13, $P<0·02$). Protein breakdown was insignificantly different.

These data suggest that in normal fasting man a mixture of amino acids, low dose glucose and fat emulsion (tolerated by peripheral veins) will support protein synthesis as effectively as amino acids and high dose glucose given centrally.

PICOU D. and TAYLOR-ROBERTS T. (1969) The measurement of total protein synthesis and catabolism and nitrogen turnover in infants in different nutritional states and receiving different amounts of dietary protein. *Clin. Sci.* 36, 283–296.

SIM A. J. W., WOLFE B. M., YOUNG V. R. et al. (1979) Glucose promotes whole-body protein synthesis from infused amino acids in fasting man. *Lancet* 1, 68–71.

35. Deleterious effect of glucagon therapy on the liver after hypotension

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Intravenous glucagon has been recommended to increase portal vein flow and oxygen delivery to the liver after periods of hypotension. It is also known that glucagon increases oxygen consumption of hepatocytes. The net effect of these antagonistic actions has not been well characterized.

In 20 dogs, hypotension was established by bleeding (mean arterial pressure 50 mmHg for 90 min followed by 35 mmHg for 30 min). Shed blood plus saline were used for resuscitation. Oxygen delivery [hepatic artery flow+portal vein flow × O_2 content] was measured using a standard technique. Liver biopsies were frozen in liquid nitrogen for determination of adenosine triphosphate (ATP), glucose and lactate. Randomly selected dogs received glucagon (6 μg/kg) as part of their regimen.

As anticipated, glucagon increased portal vein flow. Despite the increase in oxygen delivery and glucose availability after glucagon, a sustained significant ($P<0·05$) decrease in ATP was noted in the glucagon-treated animals. The equal and decreasing lactate concentration after resuscitation indicates that aerobic metabolism and tissue perfusion were adequate after resuscitation and that cytochrome function was intact. The authors postulate a direct, as yet unexplained, effect of glucagon on oxidative phosphorylation. Until this is clarified, there is little indication for glucagon therapy to augment liver perfusion after trauma.

	Baseline	End shock	30 min after resuscitation	240 min after resuscitation
No glucagon ($n=11$)				
ATP (μM/g)	2·38	0·72	1·65	1.91
Glucose (μM/g)	5·14	17·5	9·20	3·53
O_2 delivery (ml/min)	81·9	12·5	77·6	53·3
Lactate (μM/g)	1·54	12·04	13·38	6·51
Glucagon ($n=9$)				
ATP (μM/g)	2·42	0·47	0·94	0·86
Glucose (μM/g)	5·23	18·13	45·41	4·80
O_2 delivery (ml/min)	86·4	30·7	142·8	56·1
Lactate (μM/g)	2·75	13·98	18·72	11·63

36. The effect of smoking and diet on late failures after arterial reconstruction

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Two hundred prospective consecutive patients were followed at 6-monthly intervals for 5 years. Their preoperative fasting triglyceride, cholesterol, lipoprotein, fibrinogen, uric acid and carboxyhaemoglobin levels were raised compared with normal controls. Of the 200 patients, 21 had a sympathectomy only and 179 had a reconstruction. Of the latter, 18 reconstructions failed within 3 months, 20 died, 19 were lost to follow-up, 25 reconstructions failed after 3 months and 97 operations were patent after 5 years. Lipid abnormalities were randomly allocated to be left untreated or controlled by diet.

Although dietary control was successful, fasting haematological data from 1296 patient visits has conclusively shown that triglyceride, cholesterol, lipoprotein, fibrinogen and uric acid levels are the same in the late reconstruction failure group as in the successful group. However, carboxyhaemoglobin levels are seen to be significantly higher in the late failure group.

We conclude that in these patients late graft failure is associated with continued heavy cigarette smoking and there is no evidence that successful dietary control of lipoprotein abnormalities has influenced the late outcome of arterial reconstructions.

37. Increased diastolic time: an independent factor for the beneficial effect of propranolol in patients undergoing coronary bypass surgery

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Continuation of propranolol through coronary bypass surgery (CBS) decreases the incidence of subendocardial infarction and postoperative supraventricular tachycardia (Boudoulas et al., 1978). Since subendocardial flow and flow distal to a significant coronary obstruction occurs almost entirely in diastole (Brown et al., 1974) an increase in diastolic time (DT) due to propranolol may increase subendocardial flow. DT, calculated as the cycle length (RR) minus electromechanical systole (QS_2), has a non-linear relationship to heart rate (HR) increasing rapidly as rates fall below 75 (Boudoulas et al., 1978). DT, 15 h before and 2 weeks after CBS, was compared in 50 patients who underwent CBS not on propranolol (group 1) and 30 patients maintained on propranolol through CBS (mean daily dose 155±11 mg preop. and 68±9 mg postop.) (group 2).

	Before CBS		After CBS	
	Group 1	Group 2	Group 1	Group 2
HR (beats/min)	81±2	62·8±2*	95±2	73±2*
DT (ms/beat)	396±16	575±25*	339±12	426±12*

Values are ±s.e. mean.

Difference between the groups $P<0·05$.

Since sinus tachycardia is common in the early post-CBS period, the acute effect of propranolol on DT was studied in an additional 14 such patients; propranolol 2·5 mg intravenously decreased HR (−19±2 [$P<0{\cdot}01$]) and increased DT (+158±23 ms [$P<0{\cdot}01$]). Chronic propranolol treatment or acute i.v. administration significantly increased DT/beat before and after CBS; this results in a longer time for coronary perfusion. Therefore, in addition to reducing myocardial oxygen consumption, propranolol may also improve myocardial oxygen delivery by increasing subendocardial flow and thus prevent subendocardial ischaemia.

BOUDOULAS H., SNYDER G. L., LEWIS R. P. et al. (1978) Safety and rationale for continuation of propranolol therapy during coronary bypass operation. *Ann. Thorac. Surg.* **26**, 222–227.

BOUDOULAS H., RITTGERS S. E., LEWIS R. P. et al. (1979) Changes in diastolic time with various pharmacologic agents. *Circulation* **60**, 164–169.

BROWN G., GUNDEL W., GOTT V. et al. (1974) Coronary collateral flow following acute coronary occlusion: a diastolic phenomenon. *Circ. Res.* **8**, 621–631.

38. A method for studying the carotid sinus baroflex in conscious rabbits

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It has not hitherto been possible to study, in conscious animals, the control of the circulation by the arterial baroreceptor reflexes. We have studied the carotid sinus baroreflex in rabbits after implanting a rigid capsule around an innervated carotid sinus. The opposite carotid sinus was denervated and both aortic nerves cut. Pressure within the capsule could be varied within the range of ±150 mmHg. The response of the blood pressure (MAP) and heart rate or its analogue the R–R heart interval to the induced changes in carotid sinus transmural pressure (CSTMP) has been studied. For the analysis of the results we have developed a curve-fitting programme which will describe the sigmoid stimulus-response curve and provide best estimates of both the limiting values of the curve and the maximum slope of the line. This latter value represents the sensitivity or gain of the reflex.

The capsules have been successfully implanted in 18 rabbits and the characteristics of the stimulus-response curve studied. In 11 of the animals the gain was a median 0·96 (range 0·64–2·28) mmHg/mmHg and the range of ΔMAP was a median 61 (47–30) mmHg. In the remaining 7 rabbits the values for gain and range were lower and the presence of additional functioning baroreceptors was demonstrated subsequently.

39. Effects of crossclamping of descending aorta

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The preferable techniques for surgical procedures requiring crossclamping of the descending aorta are still controversial. Two of these techniques were investigated in this study. In two groups of dogs the left atrial (LA), central venous (CV), carotid artery (CA), femoral artery (FA) and femoral vein (FV) pressures, urine output, thermal dilution cardiac output and ascending aorta, renal artery (RA) and CA blood flows were constantly recorded. Group 1 dogs were placed on FV to FA partial cardiopulmonary bypass, the descending thoracic aorta was then crossclamped and the initial flow of 60 ml min^{-1} kg^{-1} was adjusted to maintain the aorta precrossclamping LA pressure. The bypass was continued for 90 min. In group 2 dogs the descending aorta was similarly crossclamped without the use of bypass and the LA pressure and peripheral vascular resistance (PVR) proximal to the clamp were maintained at their pre-crossclamping levels by intravenous drip of sodium nitroprusside. The crossclamping of the aorta was maintained for 90 min. Blood samples were drawn every 30 min for the determination of epinephrine and plasma renin activity in both groups. LV, kidney and lung biopsies were obtained for electron microscopic studies 24 h postoperatively, at sacrifice. Mean stroke work (SW) and PVR for both groups were within 1 s.d. of each other during the 90 min aortic crossclamp period. CA, LA, CV and FV pressures could be maintained at baseline pre-crossclamp levels but renal blood flow decreased by approximately 60 per cent and there was no urine output during aorta crossclamping in both groups. The mean FA pressure in group 2 dogs decreased approximately 80 per cent. Plasma norepinephrine increased similarly in both but the increase of the epinephrine in group 2 was greater.

This study suggests that FV to FA partial cardiopulmonary bypass or i.v. infusion of sodium nitroprusside can be used with the same degree of safety during aorta crossclamping as long as the LA pressure and PVR are maintained at the preclamping level.

40. Transfer function analysis of common femoral artery Doppler waveforms

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The shapes of Doppler velocity-time wave forms obtained from the common femoral arteries of 44 limbs were defined by transfer functions (TF) damping, which is derived from Fourier analysis of the wave form shape, and is a sensitive indicator of proximal arterial stenosis (Skidmore and Woodcock, 1978).

Of 22 limbs with exercise or resting ischaemia and iliac artery stenoses shown by single-plane translumbar aortograms, TF damping (mean±s.d.) was significantly greater for major stenoses (minimum angiographic diameter <5 mm) than for minor stenoses of minimum diameter 5–8 mm (0·7±0·15 *v.* 0·5±0·07; $P<0{\cdot}001$, Mann–Whitney). Pulsatility index was also calculated but failed to discriminate between the two groups. A significant inverse relationship between TF and the degree of stenosis was established ($r=-0{\cdot}75$; $P<0{\cdot}000003$) so that minimum iliac artery diameter could be calculated from individual TF values.

Eleven age-matched asymptomatic control limbs (mean age 58 years) had less TF damping (0·38±0·05; $P<0{\cdot}001$) than the symptomatic limbs, and 11 younger normal subjects (mean age 32 years) have even less TF damping (0·31±0·03).

These results suggest that common femoral TF is a more sensitive measure of iliac artery stenosis than PI, and that TF and the degree of proximal artery stenosis are closely related. The increase in TF with age in normal subjects is of interest since it may indicate the progression of early atheromatous changes within the arterial wall.

SKIDMORE R. and WOODCOCK J. P. (1978) Physiological significance of arterial models derived using transcutaneous ultrasonic flowmeters. *J. Physiol.* **277**, 29–30P.

41. Effectiveness and limitation of intra-aortic balloon counterpulsation in myocardial infarction in swine

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Intra-aortic balloon pumping (IABP) can reduce myocardial infarct size (MIS) in dogs, but this phenomenon may be secondary to pre-existing collaterals. This study describes haemodynamic changes, quantitates and qualifies myocardial infarction (MI) 24 h after coronary occlusion in swine, with and without IABP.

Twelve pigs had ligation of the LAD distal to the first diagonal branch. Six underwent 24-h treatment with IABP, beginning 45 min after occlusion. Haemodynamic effectiveness of IABP was analysed by switch on/off studies 1, 2, 3 and 24 h after ligation. Quantification of MIS was by histochemical staining with nitroblue tetrazolium; all infarcted areas were examined histologically.

In both groups MI reduced cardiac output (CO) (28·5 per cent) and mean aortic pressure (AOP) (20·4 per cent). Switch on/off studies showed a significant ($P<0·05$) improvement of AOP (4–6 per cent), CO (5–9·6 per cent) and a reduction of heart rate (4–7 per cent) during the switch on period. After 24 h, AOP in IABP animals (105±20 mmHg) was significantly ($P<0·01$) better than in controls (73±12 mmHg). MIS was 22·7±4·9 per cent of LV mass in controls and 19·4±5·9 per cent in IABP animals ($P>0·3$). Histologically, the appearance of ischaemic damage was indistinguishable between groups.

IABP is useful to stabilize and improve circulatory dynamics. However, in these controlled studies, a direct beneficial effect on acutely injured myocardium by reduction of the infarcting area could not be shown.

42. Fibrinolysis and the prediction of postoperative deep venous thrombosis

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Fibrinolytic activity (FA) was examined in 89 non-smoking control subjects using the fibrin matrix test. The mean FA was 188·4 (±71) ng fibrinolysed $ml^{-1} h^{-1}$; the distribution was normal and continuous. The formation of a deep venous thrombosis (DVT) could result from decreased fibrinolysis or could secondarily increase fibrinolysis; 28 patients undergoing elective abdominal surgery were studied to see whether DVT developed in those whose FA fell outside 2 s.d.

Eighteen were non-smokers, 10 had stopped smoking before operation. FA was estimated preoperatively, postoperatively and at 24 and 48 h. For 5 days after operation a daily ^{125}I-fibrinogen uptake scan was performed. FA was measured in ignorance of the scan results.

FA preoperatively was 226 ng $ml^{-1} h^{-1}$ (range 0–689), postoperatively 243 ng $ml^{-1} h^{-1}$ (range 12–496), at 24 h 218 ng $ml^{-1} h^{-1}$ (35–699) and at 48 h 259 ng $ml^{-1} h^{-1}$ (39–689). FA in 9 patients fell outside 2 s.d. during the study, of these 7 developed a DVT. Two patients developed a DVT when FA was within the normal range. This is significant (Fisher's exact test $P=0·002$). No single assessment time was more accurate at predicting a DVT.

Assessment of FA can predict those patients developing a DVT in most cases.

43. The saline dilution test—a preoperative predictor of DVT risk

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Certain factors, including the type of surgical operation, are associated with increased incidence of postoperative deep venous thrombosis (DVT). Recently (Janvrin et al., 1978), an association has been reported between the shortening of whole blood impedance clotting time, length of operation, rate of crystalloid fluid infusion and the postoperative DVT rate.

Preoperative blood samples were taken from 20 patients undergoing major abdominal surgery who were subsequently screened for DVT by the ^{125}I fibrinogen technique. Using the thrombelastograph, increased whole blood coagulability was demonstrated in all cases after *in vitro* dilution of the samples by 10–15 per cent with normal saline.

The 8 patients who developed a DVT had shown a mean coagulability increase of 55 per cent ± 16 per cent after *in vitro* saline dilution, whereas the 12 patients without evidence of DVT had shown a corresponding mean coagulability increase of 19 per cent ± 11 per cent. The difference between these mean values is highly statistically significant ($P<0·001$).

Of 10 patients with a coagulability increase on dilution of more than 30 per cent, 8 developed DVT, while none of the 10 patients with an increase of less than 30 per cent did so.

Thus, a single, rapid, preoperative *in vitro* test has identified those patients at risk of developing DVT after comparable abdominal surgery.

JANVRIN S. B., UR A. and GREENHALGH R. M. (1978) Postoperative deep vein thrombosis, an association with haemodilution. *Br. J. Surg.* **65**, 825.

44. Fluorocarbon emulsions as a blood substitute: effect on the omental microcirculation

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Red blood cell (RBC) velocity, vessel diameter and arteriolar pressure were determined in the microcirculation of the rabbit omentum after isovolaemic blood replacement by means of different fluorocarbon emulsions. The measurements were carried out at different haematocrit levels utilizing television techniques *in situ*.

The administration of a 15 per cent (by volume) $C_8F_{17}B_r$ or FC-47 fluorocarbon emulsion caused a slight drop of the mean arterial pressure, temporary arteriolar constriction, temporary decrease of arteriolar pressure and a localized decrease of RBC-velocity in postcapillaries and collecting venules.

Table I: VALUES IN POSTCAPILLARIES BEFORE AND AFTER BLOOD SUBSTITUTION BY MEANS OF DIFFERENT FLUOROCARBON EMULSIONS

	Control	Blood exchange 30 ml/kg BW
10% FC-43 ($n=7$)		
Hct (%)	41·2±0·8	24·8±1·4
P_A (cmH_2O)	49·5±4·1	52·0±9·9
V_{RBC} (mm/s)	1·2±0·1	1·3±0·2
15% $C_8F_{17}B_r$ ($n=7$)		
Hct (%)	42·8±1·5	29·[illegible]±1·4
P_A (cmH_2O)	45·7±1·5	40·0±4·2
V_{RBC} (mm/s)	0·8±0·1	0·4±0·1
15% FC-47 ($n=7$)		
Hct	48·2±2·0	27·7±3·6
P_A (cmH_2O)	44·2±6·3	36·6±8·4
V_{RBC} (mm/s)	1·0±0·2	0·5±0·1

Mean values±s.e. mean.

Hct, Haematocrit; P_A, arteriolar pressure; V_{RBC}, erythrocyte velocity.

Damage of endothelial cells, as suggested by augmented sticking of leucocytes along the wall of collecting venules, and destruction and conglomeration of red blood cells, were consistently observed in capillaries after injection of both of the 15 per cent fluorocarbon emulsions, whereas the injection of a 10 per cent FC-43 emulsion did not induce any significant macrohaemodynamic and microvascular alterations.

Our findings indicate that higher concentrated fluorocarbon emulsions cause deterioration of microhaemodynamic function and damage to endothelial and blood cells.

It is concluded that the fluorocarbon emulsions tested do not yet fulfil the basic requirements for a blood substitute.

45. Release of lysosomal hydrolases during extracorporeal circulation

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Contact with synthetic surfaces results in platelet adhesion and release of granule contents. This study demonstrates that during extracorporeal circulation, release of lysosomal hydrolytic enzymes occurs concomitantly. When fresh, heparinized human blood (500 ml) was recirculated for 2 h at 1000 ml/min at 37 °C in silicone rubber circuits ($n=16$) containing a membrane oxygenator (0·85 m^2), plasma levels of the platelet specific protein LA-PF4 rose from <0·5 to 15±2 μg/ml plasma ($P<0·01$), indicating extensive release of platelet α-granule contents. Concurrently, plasma activity of the lysosomal hydrolytic enzyme, N-acetyl-B-glucosaminidase, increased fourfold to 30±5 pmol substrate hydrolysed $ml^{-1} min^{-1}$ ($P<0·01$). Absorbed albumin, which decreases polymer surface affinity for platelets, and prostaglandins E_1 and E_2, which are potent inhibitors of platelet function, prevented release of LA-PF4 but failed to alter hydrolase release. Lidocaine (10 μg/ml), however, a membrane stabilizing agent, effectively inhibited lysosomal enzyme release without altering secretion of LA-PF4. The fact that platelet inhibitors failed to block secretion of lysosomal enzymes while lidocaine effectively prevented hydrolase release without altering LA-PF4 secretion suggests that leucocytes, not platelets, are the source of released lysosomal enzymes. Release of hydrolytic enzymes during cardiopulmonary bypass may cause endothelial cell injury and thus contribute to the increased vascular permeability associated with extracorporeal circulation.

46. Platelet preservation during cardiopulmonary bypass with prostaglandins

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The postoperative bleeding tendency in cardiac surgery is associated with decreased platelet numbers and impaired platelet function. During CPB the platelets adhere to the non-physiological surfaces and are continuously induced to aggregate, which leads to impaired function and to thrombocytopenia. The capacity of the potent platelet inhibiting drugs prostaglandin E_1 (PGE_1) and Prostacyclin (PGI_2) to prevent platelet aggregation during CPB and to preserve platelet function and numbers for optimal haemostasis after CPB was studied in canine experiments. In the control experiments ($n = 6$) using a bubble oxygenator, platelet numbers decreased postoperatively to 43 per cent of their preoperative value ($241 \pm 31 \cdot 10^9$/l). With PGE_1 treatment ($n = 6$), given during CPB, platelet numbers could be maintained at 74 per cent ($P < 0.02$) and with PGI_2 treatment ($n = 6$) even at 93 per cent ($P < 0.01$). Differences remained significant until the third postoperative day.

Platelet function (ADP induced aggregation) decreased in the control experiments to about 20 per cent shortly after CPB. With prostaglandin treatment platelet function was effectively inhibited during CPB but restored shortly thereafter in both groups to 70 per cent of the preoperative value ($P < 0.01$). Bleeding times, 2 h after CPB, were severely lengthened (>15 min) in the control group, while in the treated groups only slightly prolonged (6< min) values were observed.

In conclusion, administration of PGE_1 or PGI_2 during CPB can protect platelets to a large extent from irreversible damage and has great promise for clinical application in CPB to preserve optimal haemostasis.

47. Preoperative ^{99}Tc^{m}-antimony sulphide colloid scintigraphy for identification of the lymph drainage in patients with malignant melanoma

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The direction of lymphatic drainage from skin tumours, especially those situated on the trunk, is variable. Lymphangiography, because of technical problems, is not always possible. An alternative technique is scintillation camera imaging after subcutaneous injection of ^{99}Tc^{m}-labelled antimony sulphide colloid (Aspergren et al., 1978). This method has been assessed in 9 patients with malignant melanoma, 5 on the trunk and 4 on the lower limb. A subcutaneous injection of 0·5 ml colloid (particle size 5–15 mm) was made around the scar of the excised trunk melanoma and on the dorsum of the foot of the limb melanoma. As a control, a similar injection was performed on the other side of the body. The uptake of the colloid by regional lymph nodes was monitored by sequential images taken at 15-s intervals. Further pictures were taken 4 h after the injection. A block dissection of the regional lymph nodes was performed within 24 h of the study; the radioactivity of each node was measured, and correlated with the histopathology.

Radioactivity was detected in regional lymph nodes 15 min after injection. Reduced uptake, compared with the contralateral side, suggested metastases. The rate of uptake by the nodes was higher on the affected side in half the patients. The uptake by the individual node was 2–5 per cent. The total uptake of diseased nodes was reduced at 4 h and at the time of operation.

It is concluded that lymphoscintigraphy is a practical method of assessing lymph node metastases in patients with malignant melanoma.

ASPERGREN K., STRAND S. E. and PERSSON R. B. R. (1978) Quantitative lymphoscintigraphy for detection of metastases to the internal mammary lymph nodes. Biokinetics of ^{99}Tc^{m} sulphide colloid uptake and correlation with microscopy. *Acta Radiol. Oncol.* **17**, 17–26.

48. The relationship between hormone receptors and cell kinetics in breast tumour

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The potential growth rates in breast carcinomas have been investigated and the results related to the presence of hormone receptors.

Tumour fragments, 1 mm^3, were incubated with ^{3}H thymidine under hyperbaric conditions. The uptake of the radioactive label by the tumour was detected by autoradiography and a thymidine labelling index (TLI), which represents the percentage of epithelial cells labelled, was calculated. Oestrogen (ER) and progesterone (PR) receptors were determined by the dextran-coated charcoal technique. The results were compared by *t* tests.

The mean TLI in 56 tumours investigated was 5·11 per cent. In tumours without receptors (ER−, PR−) the mean TLI was 10·85 per cent. This was significantly higher ($P < 0.001$) than the mean TLI of 1·63 per cent in tumours that had both receptors present (ER+, PR+). An initial analysis had shown that ER+ tumours with levels of receptor below 50 pmol/g protein had a TLI with a mean of 3·59 per cent. A similar intermediate range of TLI with a mean of 4·23 per cent was found in ER+, PR− tumours.

These results confirm those of the previous report (Meyer et al., 1977) that tumours with low or absent levels of ER had high cellular proliferation rates. Our study shows that by using both PR and ER the tumours can be divided into groups with high (ER−, PR−), low (ER+, PR+) and intermediate (ER+, PR−) rates of cellular proliferation.

The high TLI, reflecting a high potential growth rate in tumours without receptors, may explain in part that early breast tumours without ER are associated with early recurrence.

MEYER J. S., RAO RAMANATH B., STEVENS S. C. et al. (1977) Low incidence of oestrogen receptor in breast carcinomas with rapid rates of cellular replication. *Cancer* **40**, 2290–2298.

49. A central mechanism for anorexia in cancer—role of the neurotransmitter, serotonin

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Anorexia in malignant neoplastic disease is an early sign and may occur before the development of a significant host tumour burden, suggesting a central mechanism that interferes with appetite and satiety regulation. Recent (neuropharmacologic and neurophysiologic) studies have established the role of serotonin (5HT), a neurotransmitter and product of tryptophan (TRP), in the regulation of feeding behaviour.

In the following study, TRP and 5HT metabolism and anorexia were studied in tumour-bearing rats. Three groups of rats (80–100 g) were used.

Walker 256 carcinosarcoma cells were injected into the hind limb (group 1) and saline into controls (groups 2 and 3). Groups 1 and 2 were freely fed while group 3 was pair-fed the same amount of food eaten by group 1 the previous day. Animals were sacrificed 10 days after injection; blood and brain amino acids, brain serotonin turnover and factors influencing this were measured. Voluntary food intake in group 1 decreased as early as 3 days after injection, at which time the tumour was not palpable. Plasma TRP was decreased in group 1 *v.* group 3 (67 *v.* 86 mmol/l, $P<0{\cdot}001$). However, brain TRP was normal in group 1 (21±1 nmol/g) instead of decreased as one would have expected according to the low plasma levels. In group 3, however, brain TRP values were low and in concordance with expected values: 14±1 nmol/g; $P<0{\cdot}001$. Brain serotonin metabolism was proportionally altered with TRP levels. From serotonin point of view, the tumour rats were 'satiated' (or anorectic) while the pair-fed animals were 'hungry'. The mechanism of increased brain TRP in tumour rats related to increased plasma free TRP secondary to decreased albumin and increased free fatty acid levels.

Preliminary results on decreasing brain serotonin activity in subsequent experiments, proved to increase food intake. These findings may convert the problem of anorexia in cancer to a treatable condition.

50. Circulating breast tumour antigen-sensitive T lymphocytes in early breast cancer and high risk benign breast disease

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51. Ultrasonography in the diagnosis of breast disease

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Ultrasound examination of the breast using purpose-designed machines has been shown to give a diagnostic accuracy similar to X-ray mammography (Pluygers et al., 1977). This study was undertaken to determine if standard machines could give a similar accuracy in a group of 132 unselected referrals (carcinoma 30, biopsy-proved benign disease 36, normal 66). Seventy of these patients had X-ray mammography (carcinoma 21, biopsy-proved benign disease 15, normal 34).

The ultrasonographic criteria of malignancy were sharp definition and irregularity of the margins of the lesion, internal inhomogeneity, low reflectivity, strong beam attenuation and disturbance of surrounding anatomy. The lesion was reported as being definite cancer, suspicious of cancer, benign, a simple cyst or normal. The usual criteria for cancer were used in mammography (Gallagher and Martin, 1969), and a similar reporting scheme adopted.

Ultrasound diagnosed 26 of 30 cancers (86 per cent), and 2 were suspicious of cancer (total detection rate 93 per cent). One cancer was reported as benign and the other was not detected (tumour 5 mm diameter, also missed by mammography). The mammographic results were definite cancer 15 (71 per cent), suspicious of cancer 4 (86 per cent) and 2 not detected. All cysts were correctly diagnosed by ultrasound.

It is concluded that ultrasound examination of the breast is as accurate as X-ray mammography, and has the advantage of avoiding exposure to radiation.

GALLAGHER S. H. and MARTIN J. E. (1969). The study of mammary carcinoma by mammography and whole organ sectioning. *Cancer* **23**, 855–873.

PLUYGERS S. E., ROMBAUT M., BEAUDUIN M. et al. (1977) Possibilités, résultats et indications de l'échographie mammaire. *J. Belge Radiol.* **60**, 181–196.

52. Effect of jaundice on post-cholecystectomy bile lipid secretion

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The bile lipid secretory response to interruption of the enterohepatic circulation following cholecystectomy, exploration of the common bile duct and T tube drainage has been studied in 14 patients with preoperative jaundice (group J) (serum bilirubin 23–335 μmol/l) and in 14 non-jaundiced patients (group NJ). Twenty-four hour bile volumes were collected for up to 12 days after operation and analysed for individual and total bile salts (BS), cholesterol (CH) and phospholipid (PL).

There was no significant difference in the daily bile volumes of the two groups. However, group NJ secreted increasingly higher amounts of BS, CH and PL than group J. The increased total bile salt output was due to the presence of primary bile salts, indicating increased hepatic synthesis. Maximum bile lipid outputs usually occurred after the sixth postoperative day and were significantly higher in group NJ. The mean daily output of all three bile lipids increased linearly from the second postoperative day in both groups, but the rates of increase (regression coefficients, *b*) in μmol 24 h^{-1} d^{-1} were significantly higher in group NJ.

	Maximum output (mmol/24 h) mean±s.e. mean	Rank sum test
BS		
NJ ($n=14$)	9·45±0·96	$P<0{\cdot}002$
J ($n=14$)	3·14±0·35	
CH		
NJ ($n=11$)	1·75±0·18	$P<0{\cdot}002$
J ($n=12$)	0·66±0·07	
PL		
NJ ($n=9$)	2·37±0·33	$P<0{\cdot}002$
J ($n=11$)	0·79±0·10	

	Rate of increase in output (μmol/24 h^{-1} d^{-1}) b+s.e. mean	t test
BS		
NJ ($n=14$)	808±100	$P<0{\cdot}001$
J ($n=14$)	262±34	
CH		
NJ ($n=11$)	104±20	$P<0{\cdot}001$
J ($n=12$)	14±8	
PL		
NJ ($n=9$)	154±35	$P<0{\cdot}02$
J ($n=11$)	66±10	

The results suggest an impairment in the reserve for hepatic synthesis and/or secretion of bile lipids in patients with jaundice due to large duct obstruction and indicate the need for early surgical decompression.

53. Portacaval shunt and arterialization of the liver: haemodynamic investigations and clinical results

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The clinical experience of arterialization of the liver reported by other centres has not given clear information on three important points: selection of the patients who could benefit from the procedure, operative mortality in emergency cases, length and quality of survival.

A programme of peroperative haemodynamic investigation was developed which included recording of (*a*) pressure in the portal vein—free portal pressure (FPP), maximum perfusion pressure (MPP), hepatic arterialized portal pressure (HAPP); (*b*) corrected sinusoidal pressure (CSP) at various stages of operation—the difference between the values recorded with the portal vein open or occluded gave the ΔCSP; (*c*) flow in the hepatic portal bed before (Q_{pv}) and after ($Q_{art\text{-}pv}$) portacaval shunt with arterialization (PCS-ART); (*d*) resistance of the hepatic portal bed which was calculated from the data of flow and pressure. This programme was achieved in 28 patients whose results are studied. The second part of the study was conducted between September 1973 and November 1978: 51 patients (27 elective and 24 emergency) were found at peroperative investigation to have a high residual portal flow and were submitted to PCS-ART; the operative mortality, long term survival and encephalopathy were recorded in this group.

Haemodynamic results: the flow and pressure recordings allowed separation of patients in two subgroups: (*a*) stagnant portal flow (6 patients): Q_{pv} = 83±27 ml/min; MPP =

$4{\cdot}4\pm1{\cdot}7$ cmH$_2$O; ΔCSP $= 0{\cdot}67\pm0{\cdot}33$ mmHg; (*b*) high portal flow (22 patients): $Q_{PV} = 538\pm50$ ml/min; MPP $= 25\pm1{\cdot}7$ cmH$_2$O; portal bed resistance $= 2{\cdot}45$ dyn s^{-1} cm^{-5}. There was a good correlation between the portal flow and (*a*) the MPP ($r = 0{\cdot}72$; $P<0{\cdot}001$, (*b*) the ΔCSP ($r = 0{\cdot}86$; $P<0{\cdot}001$). After arterialization, which was reserved for patients of subgroup (*b*), the flow and the pressure in the hepatic portal bed were reduced by one-third ($Q_{art-PV} = 354\pm35$ ml/min; HAPP $= 30{\cdot}5\pm1{\cdot}2$ cmH$_2$O) while the ΔCSP remained unchanged ($14{\cdot}6\pm0{\cdot}92$ mmHg) as well as the resistance of the hepatic portal bed ($2{\cdot}65$ dyn s^{-1} cm^{-5}).

Clinical results: Operative mortality was not affected in elective cases but was drastically reduced in emergency cases (17 per cent). In patients operated electively, the actuarial survival rate remained at 85 per cent from the first to the sixth postoperative year; in patients operated on as an emergency, the survival rate dropped from 73 to 67 per cent from the first to the third postoperative year to stabilize at 52 per cent from the fourth to the sixth postoperative year. Among 31 long term survivors (over 6 months), severe encephalopathy was almost exclusively seen in alcoholics who resumed drinking (16 per cent). These results are significantly better than those of a previous group of 48 patients submitted to PCS alone (23 elective, 25 emergency).

54. The role of histamine in biliary tract motor function in the primate

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The importance of histamine in gastric secretion is well documented but a possible role for histamine as a mediator of biliary motor function has not yet been appreciated. Unpublished *in vitro* experiments in our laboratory demonstrated that histamine causes contraction of guinea-pig gallbladder muscle by stimulation of H$_1$-receptors; administration of an H$_2$-agonist produced relaxation. Studies presented here demonstrate that histamine influences gallbladder pressure (GBP) and choledochal sphincter resistance (CSR) in a reciprocal manner.

Awake baboons were used to measure changes in GBP and CSR in response to histamine, its agonists and antagonists.

Intravenous histamine increases GBP with a parabolic dose–response relationship ($n = 416$). Pretreatment with the H$_1$-antagonist diphenhydramine depressed the response to histamine at all doses ($n=81$; $P<0{\cdot}001$). Pretreatment with the H$_2$-antagonist metiamide increased the response to histamine ($n = 199$; $P<0{\cdot}005$). The H$_1$ agonist 2-pyridylethylamine (PEA), given intravenously, elevated GBP in a parabolic dose–response relationship. The H$_2$-agonist (S-(3-(N,N-dimethylamino)propyl) isothiourea (dimaprit) did not change GBP in the doses studied.

A 10-min infusion of histamine decreased CSR ($n = 5$; $P<0{\cdot}05$) with a concomitant rise in GBP. Intravenous infusion of PEA increased GBP but did not change CSR. While histamine's ability to raise GBP is mediated by H$_1$-receptors, the concomitant fall in CSR is probably mediated by H$_2$-receptors.

These data demonstrate well-defined biliary motor responses to histamine and its H$_1$ and H$_2$ components; they suggest a physiologically important role in coordinating biliary responses.

55. The choledochal pressure profile in normal and postoperative conditions; an experimental study in 36 mongrel dogs

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In clinical urology urethral pressure measurement has become a valuable method in detecting urethral obstruction or incontinence of the sphincter. In biliary surgery peroperative radiomanometry has been studied comprehensively. In order to evaluate manometry as an eventual clinical method, to be used pre- and peroperatively, choledochal pressure manometry (CPR) was performed in 15 (anaesthetized) mongrel dogs. In accordance with the standards, advised by the International Continence Society, electronic pressure measurements were made with a 6 French polyethylene catheter, supplied with two side holes and perfused with 2 ml of saline per minute. This catheter was withdrawn with a constant velocity of 7 mm/min. The pressure profiles were analysed every 5 mm, the duodenal pressure being taken as a reference point. The mean normal pressure amounted to $10{\cdot}9\pm2{\cdot}2$ mmHg (mean ± s.e. mean). At the choledochoduodenal junction a statistically significant biphasic rise of pressure was recorded, $59{\cdot}8\pm8{\cdot}5$ and $54{\cdot}3\pm7{\cdot}2$ mmHg. The total length of the biphasic graph was $5{\cdot}5\pm0{\cdot}3$ cm, the distal peak measured $1{\cdot}6\pm0{\cdot}1$ cm. The proximal peak was located at $3{\cdot}7\pm0{\cdot}3$ and the distal at $1{\cdot}0\pm0{\cdot}1$ cm from the orifice of the papilla. This study in normal common bile ducts was continued with a second investigation in 21 animals, divided into three groups. In group 1 (8 animals) the sphincter was dilated. In group 2 (5 animals) sphincteroplasty was performed, while group 3 (8 animals) had a diathermic sphincterotomy. In all groups the treatment was followed by a distinct decrease in height and length of the pressure profile; all measurements were repeated after a period of 2 months. In the first group dilatation was followed by a decrease of pressure from $55{\cdot}5\pm7{\cdot}5$ to $12{\cdot}9\pm5{\cdot}8$ mmHg and of length from $5{\cdot}2\pm1{\cdot}1$ to $1{\cdot}6\pm0{\cdot}5$ cm. After 2 months the values increased significantly to about half of the initial data. Also in the second group length and pressure decreased significantly. After 2 months the pressure amounted to $9{\cdot}2\pm3{\cdot}4$ mmHg and $1{\cdot}7\pm0{\cdot}4$ cm. In the third group diathermic sphincterotomy resulted in a pressure fall to $8{\cdot}5\pm4{\cdot}1$ mmHg and a length of $1{\cdot}7\pm0{\cdot}4$ cm ($P<0{\cdot}05$). After 2 months these values were $19{\cdot}6\pm7{\cdot}3$ mmHg and $1{\cdot}3\pm0{\cdot}2$ cm respectively. The functional data correlate well with the morphological structure as studied with histology, microradioangiography and polymeric casts. The present study shows that CPR can give valuable information on pressure, length and form of the profile of the sphincter. Surgical intervention is followed by a loss of the biphasic character of the graph. The values obtained in groups 2 and 3 show that both methods give an effective decrease of length and pressure. The technique can be performed during endoscopy in man.

56. Kinetics of BSP clearance as the most reliable criterion of the hepatic dysfunction after jejuno-ileal bypass in the rat

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Hepatocellular failure is the most serious complication of intestinal bypass surgery. Numerous aetiologic factors have been advanced to explain these lesions but the criteria used are not quite reliable. The purpose of this work is to establish the best parameter of hepatic dysfunction in the adult Wistar rat and to correlate its variations with the evolution of the intestinal adaptation.

Two hundred and forty-four adult Wistar rats, weighing 290 g, were randomly divided into two groups. After ether anaesthesia, group 1 (123 rats) was submitted to a 90 per cent small intestinal bypass with an end to end jejuno-ileal anastomosis. The excluded loop was closed and the distal extremity anastomosed end to side to the sigmoid. Group 2 (121 control rats) was sham-operated. The studies were performed every 15 days until the third month after operation. The following parameters were determined as indices of liver function: kinetics of BSP clearance from the plasma; glutamic oxaloacetic transaminase (GOT); glutamic pyruvic transaminase (GPT); esterase A and C; cholinesterase C; plasma total protein and albumin. Simultaneously, the liver was examined by optic and electron microscopy. Intestinal adaptation of the included segment was studied by measuring the wet weight of the mucosa and its protein content.

There were no structural or ultrastructural changes in the liver of both groups. Animals of group 1 showed a marked decrease of plasma total proteins and albumin, which was the most pronounced at 1 month (125 per cent of control, $P<0{\cdot}01$). There was no difference in the plasma enzyme activities measured in both groups. The percentage of retention of BSP was increased in group 1 up to 2 months, the maximal increase (310 per cent of control, $P<0{\cdot}01$) being observed at 1 month. The wet weight of the ileal mucosa and its protein content, expressed per unit length, were not different up to 2 months; from this period, both parameters increased by approximately 160 per cent of control ($P<0{\cdot}05$).

These results show that BSP clearance is the most sensitive and reliable criterion of the hepatic dysfunction in Wistar rats while plasma enzyme activities were not altered after jejuno-ileal bypass. The parallelism between the variations of the BSP clearance and the absence of a sufficient intestinal adaptation lends weight to the 'nutritional' theory of hepatic lesions which occur after jejuno-ileal bypass. Indeed, within the initial postoperative period, there is a malabsorption syndrome that induces a transient malnutrition state.

57. The determination of site and severity of arterial lesions in claudicants using ^{99}Tc^{m} muscle clearance

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There has been no end to the attempts made to determine the site and severity of arterial lesions in claudicants by the use of non-invasive methods, but, so far, their diagnostic value has been limited. A method whose diagnostic accuracy in determining the site and functional severity of arterial lesions approaches that of arteriography is presented.

The hyperaemic index, which is the ratio of the total excess of blood during post-exercise hyperaemia over the maximum hyperaemic flow, has been determined in the thigh and calf simultaneously by measuring the ^{99}Tc^{m}-muscle clearance in 30 limbs of 20 healthy volunteers and 139 limbs of 145 patients with claudication. Lumbar arteriography classified the lesions in all the patients as 0–10 per cent, 10–40 per cent, 40–70 per cent, <70 per cent stenosis or occlusion.

A bivariate analysis of the hyperaemic indices of the thigh and calf determined the site and severity of single lesions with 100 per cent accuracy. In limbs with combined aorto-iliac and superficial femoral lesions the values of the hyperaemic indices could determine which of the two lesions was the more severe (100 per cent accuracy) and the degree of stenosis produced by each one (96 per cent accuracy).

These findings have been confirmed in a second blind prospective study of 44 limbs in which determination of the site and severity of lesions has preceded aortography.

58. Thromboxane A_2 regulation of renal vascular resistance

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The adverse effect on renal vascular resistance (RVR) of non-ischaemic kidneys by ischaemic kidneys when both share a common perfusate can be prevented by imidazole inhibition of thromboxane A_2(TXA_2) synthesis (Sicard et al., 1978). Paired dog kidneys were perfused on two MOX-100 machines connected to a pool of common perfusate. To an optimally harvested first kidney was added a second kidney from each of 7 groups. Group 1 (control) second kidney optimally harvested; groups 2–7, second kidney subjected to 60 min of warm ischaemia. Group 2, no additional manipulation; group 3, ischaemic kidney on perfusion for only 10 min; group 4, ischaemic kidney added after 1 h of separate perfusion; group 5, imidazole (7·5 mg/kg, i.v.) treatment of both kidneys; group 6, imidazole treatment of first non-ischaemic kidney only; group 7, imidazole treatment of second ischaemic kidney only. The percentage increase in baseline RVR of non-ischaemic first kidneys after addition of second kidneys is shown below.

	Groups						
Time (h)	1	2	3	4	5	6	7
½	3	37	29	—	2	−12	−17
1	5	56	55	−4	11	−13	11
2	5	76	69	−2	22	−12	28
3	2	86	80	—	48	−9	39

We conclude that the site of production and action of TXA_2 occurs in both kidneys but is more important in the non-ischaemic kidney since limited exposure to the initial venous effluent of the ischaemic kidney causes a sustained rise in RVR which can be most effectively blocked by TXA_2 inhibition in the non-ischaemic rather than in the ischaemic kidney. Unmasking of prostaglandin E_2 (renal vasodilatation) by TAX_2 inhibition may contribute to this effect.

SICARD G. A., ETHEREDGE E. C. and ANDERSON C. B. (1978) Modification of ischaemic renal injury by prostaglandin inhibition. *Surg. Forum* **29**, 54–56.

59. Effects of extracranial–intracranial anastomosis on cortical oxidative metabolism

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Results of 163 microanastomoses of the superficial temporal (STA) to middle cerebral artery (MCA) in patients with transient ischaemic attacks (TIA) or minor stroke show a 15 per cent to 20 per cent increase in cortical blood flow (i.v. ^{133}Xe method). To explain improvement in TIA and neurological deficit, it is also necessary to provide evidence for increased cortical oxidative metabolism. Experiments were done on 43 cats to monitor brain Po_2 (bPo_2) and the redox level of members of the electron transport chain, using N_2O/O_2 anaesthesia (FiO_2 20 per cent), with immobilization by Flaxedil, plus local skin anaesthesia, ketamine and artificial ventilation. Cortical cytochrome oxidase (Cy$_3$. a a$_3$) and flavoprotein (FP) levels were monitored by non-invasive optical techniques.

Model TIA produced by 5–30 s bilateral common carotid occlusion (CCO), caused decreased bPo_2 and reduction of Cyt. a,a$_3$ and FP. Hypotensive ischaemia (arteriotomy) or hypoxia (Fio$_2$ 10 per cent) caused decreased bPo_2 and reduced Cyt. a,a$_3$ to be greatly prolonged following a test CCO. The same monitoring techniques were used intraoperatively in 37 patients. Following anastomosis there was an increase in bPo_2 and oxidized Cyt. a,a$_3$ and FP, as well as more rapid recovery from a test change in Fio$_2$ (15 per cent). These results suggest increased cortical oxidative metabolism as the major source of clinical improvement.

60. Deep vein thrombosis and tourniquet ischaemia

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Operations on the lower limb are frequently performed in a bloodless field. However, it is not known whether the use of a tourniquet increases the likelihood of a thrombus formation by promoting venous stasis or reduces the incidence by increasing the fibrinolytic activity as a result of release of the plasminogen activator produced in the endothelium of small vessels.

Fifty-five consecutive patients (mean age 42 years, range 18–87), undergoing lower limb surgery requiring the use of a pneumatic tourniquet, were investigated. Venography was performed in each patient on the seventh postoperative day to confirm or refute the presence of deep vein thrombosis (DVT). In 13 consecutive patients, blood samples were withdrawn from an arm vein just before induction of anaesthesia, after 30 min of tourniquet ischaemia, immediately after release of tourniquet and on the second postoperative day. These were analysed for changes in the fibrinolytic activity by measuring the levels of plasminogen, fibrinogen, euglobulin lysis time (ELT), fibrinogen/fibrin degradation products (FDP), α_1-antiplasmin and α_2-macroglobulin. The operations performed included meniscectomy (37 patients), knee replacement (9 patients) and minor foot operations (9 patients). Twenty-one (38 per cent) out of 55 patients developed DVT; in patients below the age of 40 the incidence was 26 per cent and over 40 years, 50 per cent. Eighteen tibial thrombi were >5 cm, 3 of these involved the popliteal or femoral vein. One of 3 smaller thrombi (<5 cm) was associated with femoral cusp thrombosis. Of all the haematological investigations performed, the only change of significance was a prolonged ELT at 48 h ($P<0·02$).

61. A randomized trial of heparin *v.* streptokinase in the treatment of acute proximal venous thrombosis

M. S. ELLIOT and THE GROOTE SCHUUR HOSPITAL THROMBO-EMBOLUS STUDY GROUP (Introduced by J. TERBLANCHE), *Groote Schuur Hospital and the University of Cape Town* (*see* pp. 838–843)

62. What length of prepyloric stomach should be left innervated in highly selective vagotomy?

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Johnston and Wilkinson (1969) leave 6 cm (5–7) of distal stomach innervated during HSV, but Amdrup and Jensen, by the use of a pH probe were able to leave 8–10 cm (mean, 9 cm) innervated and found only half the incidence of postprandial fullness which was found in Leeds and a higher proportion of Visick grade 1 results (Amdrup et al., 1974). This might have been due to better accommodation to distension after the lesser gastric denervation. Goligher (1974) subsequently stated that he left 10–11 cm innervated.

In a prospective, randomized trial in 90 DU patients, we left 6 cm (5–7 cm) innervated in 44 patients and 10 cm (9–11 cm) innervated in 42 patients. Patients were then reviewed 'blind' in a follow-up clinic, each year for 3–6 years. Operative mortality was nil.

	6 cm	10 cm
Hollander positive test (1 week)	18% (2% early positive)	37% (21% early positive)
Recurrent ulceration (RU)	9%	13%
Epigastric fullness p.c.	24%	22%
Poor results (Visick grades 3 and 4)	18%	26%

Differences not significant except for PAO_I–BAO.

When 10 cm were left innervated, both mean PAO_I and RU were higher and more patients were suspected of having RU. Side effects of operation such as fullness, flatulence and heartburn were just as common after the more limited gastric denervation. Thus it seems preferable to leave only 5–7 cm innervated.

AMDRUP E., JENSEN H. E., JOHNSTON D. et al. (1974) Clinical results of parietal cell vagotomy (highly selective vagotomy) two to four years after operation. *Ann. Surg.* **180**, 279–284.

GOLIGHER J. C. (1974) A technique for highly selective (parietal cell or proximal gastric) vagotomy for duodenal ulcer. *Br. J. Surg.* **61**, 337–345.

JOHNSTON D. and WILKINSON A. R. (1969) Selective vagotomy with innervated antrum without drainage procedure for duodenal ulcer. *Br. J. Surg.* **56**, 626.

63. The effect of bile acids on the pancreatic duct mucosal barrier

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Back diffusion of HCO_3^- from pancreatic juice into blood is impaired by a barrier in the pancreatic duct. We previously showed that certain agents damage this barrier (Reber et al., 1979). Since pancreatitis and pancreatic cancer may be related to bile reflux into the pancreatic ducts, we studied the effects of bile acids on this barrier. We perfused the main duct in cats at 0·5 ml/h and pressure <20 mmHg, for two periods (1 and 3) using a standard perfusate (SP) (Na 150, HCO_3 120, Cl 30 mmol/l). Periods 1 and 3 were separated by period 2 when the duct was perfused with bile acid in SP. An increase in back diffusion of HCO_3^- in period 3 compared to 1 was interpreted as an increase in mucosal permeability from damage during period 2.

No. of cats	Bile acid (period 2)	Period 3 *v.* Period 1 ΔHCO_3 Flux	ΔCl Flux
10	Control	+0·09±0·08	−0·17±0·07
6	Cholic (12 g/l)	−0·15±0·06*	+0·03±0·03*
4	Glyco. (12 g/l)	−0·20±0·06*	+0·14±0·10*
6	Cheno. (11·5 g/l)	−1·45±0·31*	+1·46±0·22*
6	Glycocheno. (11·5 g/l)	−1·33±0·22*	+1·33±0·16*
9	Deoxycholic (6·7 g/l)	−1·80±0·29*	+1·46±0·21*
3	Glycodeoxy. (6·7 g/l)	−0·91±0·42*	+0·85±0·25*

Mean ±s.e. mean. *$P<0·05$.
Glyco., glycocholic; cheno., chenodeoxycholic; glycocheno., glycochenodeoxycholic; glycodeoxy., glycodeoxycholic.

All the bile acids, at physiological concentrations and pressures, damaged the pancreatic duct. This suggests that bile may cause pancreatic disease not only by directly injuring the pancreatic cells, but by increasing their permeability to other substances. The latter mechanism may be the more important one.

REBER H. A., ROBERTS C. and WAY L. W. (1979) The pancreatic duct mucosal barrier. *Am. J. Surg.* **137**, 128–134.

64. Four-year results of prospective trial for duodenal ulcer (TVP *v.* HSV)

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One hundred and forty-three patients (116 males and 27 females) with duodenal ulcer have taken part in a randomized prospective trial of truncal vagotomy and pyloroplasty (TVP) and highly selective vagotomy (HSV) organized in three Manchester hospitals. Seventy-one patients underwent TVP and 72 had HSV. Preoperative and early postoperative data were recorded by the surgeon. Late follow-up data were recorded by a physician unaware of the operation performed. An earlier analysis of the results (Manchester Ulcer Trial Group, 1977) revealed no significant difference between the groups with regard to recurrent ulceration (TVP 2·7 per cent, HSV 8 per cent) and functional results.

One hundred and thirty patients (91 per cent) have now been followed up for 2½–5½ years (mean 4 years). There have been 5 proved recurrent ulcers following TVP (7·6 per cent) and 12 after HSV (18·4 per cent). Functional results were assessed by one physician according to a Visick scale and the two groups were found to be very similar.

	Visick grading			
	1 %	2 %	3 %	4 %
TVP ($n=65$)	38 (58·4)	15 (23·0)	3 (4·6)	9 (13·8)
HSV ($n=65$)	41 (63·0)	8 (12·3)	2 (3·0)	14 (21·5)

There was significantly more diarrhoea after TVP (14 per cent) than HSV (1·5 per cent) ($P<0·025$) but no significant difference with regard to dumping, heartburn and vomiting.

There has been an increase in the incidence of recurrent ulceration in both groups since last reported but this increase is greater in the HSV group.

MANCHESTER ULCER TRIAL GROUP (1977) Prospective randomized trial of vagotomy in uncomplicated duodenal ulceration. *Br. J. Surg.* **64**, 823.

65. The effect of HSV and of SV+P on the relationship between gastric emptying and oral glucose tolerance

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It is well documented that vagotomy produces changes in the pattern of gastric emptying. However, there is little information comparing the relationship between gastric emptying and the configuration of the glucose tolerance curve. In addition there are no measurements of these two parameters in the early and late postoperative course after different types of vagotomy.

Two groups of patients were studied: group 1, patients with selective gastric vagotomy and Finney-pyloroplasty (SV+P; $n=20$; M 17; F 3; 39 yr (20–50); 65 kg (48–93); 173·5 cm (155–189)). Group 2, 19 patients with HSV (M 13, F 6; 38 yr (29–61); 65 kg (50–107); 172 cm (160–183)). In each patient 3 measurements were performed (preoperatively, 11 days (9–13) postoperatively, 3·9 months (3–24) postoperatively) of oral glucose tolerance and of the half-life of gastric emptying.

The data in the Table are given as median and range. For statistical analysis the tests of Wilcoxon and Mann–Whitney were employed.

	$T_{\frac{1}{2}}$ (min)	Blood glucose (mg/100 ml) Rate of rise (mg/min)	Peak
Group 1			
Preop.	52·5 (25–80)	1·89 (0·95–2·82)	123·6 (96·5–154·2)
Early p.o.	83 (47–370)	0·63 (0·45–2·47)	92·2 (64–170·5)
Late p.o.	46·5 (18–83)	2·66 (0·95–3·85)	126·7 (69–187)
Group 2			
Preop.	49 (28–74)	1·89 (0·93–4·15)	145 (82–200)
Early p.o.	102 (56–300)	0·36 (0·3–2·15)	89·2 (61–134)
Late p.o.	58 (25–195)	0·7 (0·25–2·5)	121 (35–174)

		Plasma insulin (u/l)	
	$T_{\frac{1}{2}}$ (min)	Fasting	Peak
Group 1			
Preop.	52·5 (25–80)	15·2 (7–28·5)	56 (21·5–175)
Early p.o.	83 (47–370)	14 (6–26.5)	22 (7·5–64)
Late p.o.	46·5 (18–83)	10 (2–64)	63·5 (20–345)
Group 2			
Preop.	49 (28–74)	11·5 (1·9–27.5)	58·7 (21–165)
Early p.o.	102 (56–300)	13·3 (6·5–35)	22 (5–54)
Late p.o.	58 (25–195)	15 (4–36)	45 (6–140)

Gastric emptying in the early postoperative period in both patient groups was significantly delayed ($P<0·01$). Glucose and insulin concentrations increased very slowly to a peak which showed only a small difference from the fasting value. In both groups the late postoperative $T_{\frac{1}{2}}$ returned towards normal. However, in the patients with SV+P the $T_{\frac{1}{2}}$ was shorter than preoperatively and was significantly shorter than in the patients with HSV ($P<0·05$). Corresponding with these results, in the SV+P patients the rate of rise of glucose concentration was greater than preoperatively and was also significantly more rapid than after HSV ($P<0·01$).

The results demonstrate that there is a close relationship between the pattern of gastric emptying and the configuration of the glucose tolerance curve. Thus the destroyed integrity of the antropyloric region in the patients with SV+P leads to both an uncontrolled gastric emptying and a precipitated increase of blood glucose concentration.

66. Distal intramural spread and local recurrence of rectal cancer

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With the advent of stapling instruments, and techniques such as transanal colo-anal anastomosis (Parks, 1972), it is technically feasible to perform sphincter-saving operations for most patients with low rectal carcinomas. If, however, the recommended 5-cm margin of distal clearance is adhered to, many of these patients will require permanent colostomies. We have therefore re-examined the relevance of the 5-cm rule.

Fifty consecutive abdominoperineal resection specimens were examined by multiple sections distal to the tumour. All lesions were situated 5–10 cm from the anal verge on sigmoidoscopy. Only 3 specimens (6 per cent) showed distal intramural spread of less than 1 cm. All 3 were poorly differentiated Dukes' C tumours.

All anterior resections performed between 1957 and 1968 were reviewed. The minimum period of follow-up was 10 years. In 82 curative operations, 32 (group 1) were resected with a distal margin greater than 5 cm (mean 7 cm) and 50 (group 2) with a margin less than 5 cm (mean 2·6 cm). The age and sex distribution was similar in both groups. Local recurrence was found in 3 patients (9·3 per cent) in group 1 (all had poorly differentiated lesions) and in 8 patients (16 per cent) in group 2 (7 poorly differentiated, 1 well differentiated). Of the 11 patients with recurrence, 9 had Dukes' C growths.

Thus a 5-cm margin of clearance is needed only in patients who have poorly differentiated tumours, most of whom are incurable because of other modes of spread.

PARKS A. G. (1972) Trans-anal technique in low rectal anastomosis. *Proc. R. Soc. Med.* **65**, 975–979.

67. Hepatoprotection by inosine and chlorpromazine from *in vivo* normothermic liver ischaemia assessed by orthotopic rat liver transplantation

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Orthotopic rat liver transplantation as a model for evaluation of liver preservation methods has been described (Jackson and Hobbs, 1977). This model has now been used to assess the ability of the purine nucleoside inosine and the drug chlorpromazine to protect the rat liver from 60 min *in vivo* normothermic ischaemia; an otherwise fatal ischaemic insult when assessed by subsequent orthotopic transplantation.

Inosine can protect rat kidneys from *in vivo* warm ischaemia (Fernando, 1976) but has no effect when renal preservation is evaluated using the isolated perfused rat kidney (Marshall et al., 1978). Chlorpromazine is an established hepatoprotectant preventing lobar ischaemic liver cell death *in vivo* (Chien, 1977).

Group	No.	*In vivo* donor ischaemia	Protectant	Survival
1	10	0–1 min	—	8
2	10	60 min	—	0
3	8	60 min	I.v. inosine	3
4	8	60 min	I.v. chlorpromazine	4
5	8	60 min	Regional hypothermia 25–30 °C	2

Hepatoprotection was obtained by inosine, chlorpromazine and regional hypothermia.

CHIEN K. R. and FARBER J. C. (1977) Prevention by chlorpromazine of ischaemic liver cell death. *Am. J. Pathol.* **88**, 539–557.

FERNANDO A. R. (1976) Enhanced preservation of the ischaemic kidney with inosine. *Lancet* **1**, 555–557.

JACKSON D. B. and HOBBS K. E. F. (1977) An animal model for the study of liver preservation. *Br. J. Surg.* **64**, 292.

MARSHALL V., ROSS B., BISHOP M. et al. (1978) Evaluation of renal preservation using the isolated perfused rat kidney. *Transplant.* **26**, 315–318.

68. Studies in renal preservation using the isolated perfused rat kidney: evaluation of citrate flushing solution

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Evaluation of renal preservation is conventionally by reimplantation of the stored canine kidney which has attendant limitations—survival is influenced by technical, anaesthetic and after-care factors. The isolated perfused rat kidney model allows rapid and economical screening of preservation methods. A standardized system provides early and repeated evaluation of organ function from serial analysis of perfusate, urine and tissue. Criteria used are urinary/plasma inulin ratio, glomerular filtrate rate, sodium and potassium reabsorption and excretion, tissue adenine nucleotide content and histology.

The validity of the model has been demonstrated by correlation of functional parameters and of adenine nucleotide content with increasing periods of prior warm and cold ischaemia. For cold flush-ice preservation of the kidney, a hyperosmolar (400 mosmol/l) solution containing citrate (HC) was demonstrated to be superior to alternative flushing solutions (Collins', Sacks' and Perfudex).

Further investigation of the effective components of the HC solution has been made by adjusting the mannitol concentration to give solutions of varying osmolality (300, 350 and 400 mosmol/l) with a constant citrate content. After cold flush with the test solutions and 24 hours' ice storage, renal function was significantly ($P<0{\cdot}01$) better maintained by the three citrate solutions than with Hartmann's solution in each case. The isomolar citrate solution gave significantly better renal function than the hyperosmolar (400 mosmol/l) solution ($P<0{\cdot}05$). Of the functional parameters tested sodium reabsorption appeared the most senstive index.

Our findings suggest that the efficacy of the HC solution in kidney preservation is due not to hyperosmolality but to specific effects of citrate and/or other components.

69. Improvement of hypothermic kidney storage preservation by using sub-zero temperatures

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The main principle of hypothermic kidney storage preservation is based on the reduction of metabolism by hypothermia. Temperatures of +2 to +4 °C are applied in clinical practice today. Theoretically, the results should become even better if metabolism is further reduced by temperatures below 0 °C. This was tried in the experiments presented here.

Bilateral nephrectomy was performed in mongrel dogs of 20–25 kg body weight. The kidneys were flushed with 500 ml of Collins' C_3-solution which contained 120 g/l saccharose (035M) and then stored in this solution for 12 ($n=8$) and 24 h ($n=7$) at −2 °C. The osmolality of the solution ranged about 770 mosmol/kg. The Na^+ concentration was 9 mmol/l, the K^+ concentration was 104 mmol/l. The temperature was controlled continuously with puncture electrodes in the medulla of the kidney to about −2 °C. The control group was stored in Collins' or Sacks' solution at +4 °C. After storage the kidneys were transplanted to the neck vessels of a recipient animal and the immediate function of the kidneys was assessed for 6 h with PAH and inulin clearances.

	Hypertonic solution at −2 °C	Control groups at +4 °C	
		Collins'	Sacks'
2 h storage:			
PAH (ml min^{-1} 100 g^{-1})	$50{\cdot}1\pm21{\cdot}1$	$50{\cdot}0\pm14{\cdot}9$	$61{\cdot}0\pm17{\cdot}4$
Inulin (ml min^{-1} 100 g^{-1})	$13{\cdot}4\pm5{\cdot}5$	$8{\cdot}3\pm3{\cdot}6$	$10{\cdot}4\pm5{\cdot}8$
	($n=8$)	($n=6$)	($n=6$)
24 h storage:			
PAH (ml min^{-1} 100 g^{-1})	$35{\cdot}9\pm19{\cdot}4$	$14{\cdot}2\pm9{\cdot}3$	$11{\cdot}4\pm13{\cdot}5$
Inulin (ml min^{-1} 100 g^{-1})	$13{\cdot}2\pm7{\cdot}1$	$2{\cdot}9\pm2{\cdot}0$	$2{\cdot}5\pm1{\cdot}9$
	($n=7$)	($n=6$)	($n=6$)

Dog kidneys can be stored successfully for 24 h in an intracellular solution at 770 mosmol/kg. If this solution is used, the kidneys do not freeze at −2 °C. Kidneys work significantly better after 24 h storage if they are stored in a hypertonic solution such as Collins' or Sacks' at −2 °C. This means that kidney metabolism can be really reduced by decreasing the temperature below 0 °C, and therefore kidneys function better after transplantation. The prerequisite for the success of this method is the use of a highly hyperosmolar solution.

70. Relevance of HLA matching and HLA-A2 to outcome in cadaveric renal transplants

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Controversy continues in the United States concerning benefits of human lymphocyte antigen (HLA) matching and the matching of any one HLA Ag in cadaver renal transplantation (Opelz, 1977). HLA-A2 matching was described as a factor in avoiding sensitization to platelet transfusions (Duquesnoy et al., 1977).

We report 64 consecutive cadaver renal transplants (January 1973–December 1978) in which HLA matching correlated strongly with kidney functional survival and matching for the common HLA-A2 Ag significantly reduced rejection loss.

Matching for 2 or more HLA Ags improved functional survival at each time interval: 6 month 39/49 *v.* 6/11; 1 year 34/42 *v.* 5/11; 2 year 20/28 *v.* 3/11; and 3 year 13/18 *v.* 1/9 ($P<0{\cdot}05$, $P<0{\cdot}01$ Fisher's exact test). This effect is most prominent in the low risk group (<45 years) where 2 to 4 Ag-matched kidneys function at 90 per cent at 1 year (28/31), 89 per cent at 2 years (17/17) and 86 per cent at 3 years (12/14).

HLA-A2 Ag-matched transplants had a lower incidence of rejection episodes during the first month (66·7 per cent *v.* 90·3 per cent χ^2 ($P<0{\cdot}05$) and a decreased cumulative rejection loss from 3/8 in HLA-A2 mismatch and 7/23 in non-HLA-A2 matches to 2/33 in the HLA-A2-matched patients ($P<0{\cdot}05$ Fisher's exact test). None of the 2 to 4 Ag-matched HLA-A2-matched patients has rejected their graft (0/30).

We conclude that for an increased chance of successful transplantation, two or more antigens should be matched in cadaver transplants and that if the recipient has HLA-A2 this antigen should be matched.

DUQUESNOY R. J., FILIP D. J. and ASTER R. N. (1977) Influence of HLA-A2 on the effectiveness of platelet transfusion in alloimmunized thrombocytopenic patients. *Blood* **50**, 407–412.

OPELZ G. (1977) Histocompatibility testing in renal transplantation. *Urology* (Suppl.) **9**, 72–81.

71. Histocompatibility matching and renal allograft survival in dogs

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With the present methods of histocompatibility matching an excellent correlation of matchgrade with human kidney allograft survival is seen in related donor-recipient pairs (DRP) but this correlation is much less clear in cadaver kidney transplantation. Experimental animal models may be helpful to clarify this discrepancy and to develop better methods for donor selection. Histocompatibility matching in dogs is performed in our laboratory by the use of serologic tests and mixed lymphocyte cultures to detect the serologically defined (SD) and lymphocyte defined (LD) antigens respectively. The genetic code for these antigens is carried by a chromosomal region called the major histocompatibility complex (MHC). Over one hundred kidneys were transplanted to test the efficacy of matching for these antigens under varying defined conditions. In some protocols standard immunosuppression was used (2 mg Imuran and 1 mg prednisolone kg BW^{-1} d^{-1}). Kidney function was considered to have ceased when serum creatinine exceeded 1000 µmol/l; histological examination of the graft was always performed.

Analysis of the data shows that better matching for SD and/or LD antigens is correlated with improved kidney allograft survival in littermate DRP, but much less so in nonlittermate DRP. In unrelated mongrels, LD, but not SD matching improves kidney allograft survival. The data obtained in immunosuppressed dogs suggest that undefined 'minor' (non-MHC) antigens are comparable in strength with the SD and LD antigens, SD+LD typing appears to have a better effect if the recipient is treated with immunosuppressive drugs. Thus histocompatibility matching and immunosuppression appear to be synergistic. Administration of third party blood transfusions prior to transplantation may also enhance renal allograft survival in immunosuppressed dogs, but it remains to be seen whether histocompatibility matching and blood transfusions have a synergistic effect too.

DRP	Imuran	Match SD	 LD
Littermate beagles	No	Id.	Id.
Littermate beagles	No	Haploid.	
Littermate beagles	No	Complete mismatch	
Non-littermate beagles	No	Id.	Id.
Unrelated mongrels	No	Id.	Id.
Unrelated mongrels	No	Non-id.	Id.
Unrelated mongrels	No	Id.	Non-id.
Unrelated mongrels	No	Non-id.	Non-id.
Littermate beagles	Yes	Id.	Id.
Littermate beagles	Yes	Haploid	
Non-littermate beagles	Yes	Id.	Id.
Unrelated mongrels	Yes	Non-id.	Non-id.

DRP	No.	Survival (d)
Littermate beagles	21	43±14 (s.d.) (3*)
Littermate beagles	10	24±14
Littermate beagles	12	16±8
Non-littermate beagles	9	28±7
Unrelated mongrels	5	18±5
Unrelated mongrels	5	16±5
Unrelated mongrels	11	10±2
Unrelated mongrels	8	10±3
Littermate beagles	7	73 (no rejection) (5*)
Littermate beagles	7	12, 12, 16, 16, 79 (2*)
Non-littermate beagles	7	(7*)
Unrelated mongrels	7	11, 12, 15, 15, 16, 16, 16, 19, 19, 19, 20, 26, 29, 30, 41, 48, >60

Id., Identical. *Grafts surviving >100 days.

72. Comparison of physiological events, high energy phosphate content and mitochondrial function during ischaemia in normal and hypertrophied hearts

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Although hypertrophied myocardium appears more susceptible to ischaemic injury during cardiac operations than non-hypertrophied myocardium, the biochemical response of hypertrophied hearts to ischaemia has not been fully elucidated. High energy phosphate levels (ATP, CP μmol/g dry weight) and mitochondrial function were determined in 75 normal and 103 hypertrophied isolated rat hearts following 15 min of Langendorf perfusion (control) at initiation of ischaemic contracture and at completion of ischaemic contracture.

Hypertrophy, produced by banding the ascending aorta 6 weeks before study, was confirmed by left ventricular (mg/g body weight) ratios (normal 1·92 wet, 0 43 dry; hypertrophy 2·69 wet, 0·59 dry). Qo_2 (nanoatoms oxygen min^{-1} mg protein^{-1}), ATP : O and respiratory control index (RCI) were calculated from isolated mitochondria polarographically. Results (mean±s.e. mean) with NAD-linked substrate are shown in next column and were similar for FAD-linked substrate.

Although ATP and CP content was consistently lower in hypertrophied hearts, mitochondria from hypertrophied hearts demonstrated significantly ($P<0·05$) higher active respiration (Qo_2) and respiratory control (RCI). Contracture initiation occurred sooner with hypertrophy but completion was delayed. These results suggest that the increased susceptibility of hypertrophied myocardium to ischaemic contracture may be due to the lower ATP stores present with the onset of ischaemia.

	Control N	 H	Contracture initiation N	 H
Qo_2	97·1±8·5	134·0±10·2	94·4±9 8	149·8±20·2
RCI	6·6±0·4	8·1±0 5	5·3±0·3	7·1±0 8
ATP	24·2±1·1	20·3±1·3	14·3±1·0	12·0±0·5
CP	33 9±2·4	28·3±2·4	6·3±0 4	2 4±0·1
Duration of ischaemia (min)			10·1±0·7	5·7±0·6

	Contracture completion N	 H
Qo_2	87·8±9·8	134·1±8·2
RCI	3·4±0·2	5·7±0·3
ATP	4·6±0·7	2·0±0·2
CP	5·2±0·5	2·4±0·1
Duration of ischaemia (min)	19·9±0·7	23·1±1·0

N, Normal; H, hypertrophy.

73. Pharmacological analysis of the mesenteric vasodilator effect of vasoactive intestinal peptide (VIP)

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Among a broad spectrum of biological activities, VIP has been shown to be a vasodilator of the intestinal vascular bed. The purpose of the present study was to analyse the mode of action of this polypeptide on the mesenteric blood vessels using a pharmacological approach.

The investigations were carried out on isolated canine jejunal loops perfused at normothermia, under pulsatile flow, with heparinized and oxygenated blood. The vascular effects were studied by analysing the changes of the vascular resistance produced by VIP (500 μg/l ≃ED$_{50}$) before and during blockage or inhibition of the β-adrenergic receptors by propranolol (5–10 mg/l of blood), the cholinergic receptors by atropine (5–10 mg/l), the dopaminergic receptors by haloperidol (10 mg/l), the prostaglandins synthesis by indomethacin (5–10 mg/l) and also during infusion of tetrodotoxin (TTx—0·25 mg/l). Except for indomethacin and TTx, the efficacy of each antagonist was tested by analysing its blocking action on the vasomotor effect of a specific agonist.

Results: 1. Propranolol inhibits 29 per cent (±7 per cent) of the vascular effects of VIP whereas at the same blood concentration it antagonizes in a proportion of 71 per cent (±9 per cent) the vasodilatation induced by isoprenaline. 2. Atropine, at concentrations which suppress 96 per cent (±6 per cent) of the vascular effect of acetylcholine, inhibits the VIP induced vasodilatation only in a ratio of 29 per cent (±8 per cent). 3. Haloperidol antagonizes the vascular effect of VIP in a proportion of 32 per cent (±5 per cent) whereas this blocking agent suppresses 53 per cent (±4 per cent) of the vasodilatation induced by dopamine. 4. Indomethacin and TTx have no effect on the vasodilator properties of VIP.

These results suggest that neither the classic nervous pathways nor the mediation by vasodilator prostaglandins intervene in the mesenteric vasodilatation produced by VIP. The partial inhibition observed in the presence of several blocking agents used may result from non-specific effects of the antagonists. The absence of any inhibitory action of TTx is not conflicting with the neurotransmitter hypothesis recently proposed for VIP, in so far as the vascular effects of this polypeptide observed in the present study correspond to a receptor stimulation of exogenous nature. All these data argue for the existence of a specific receptor for VIP at the level of the mesenteric vascular smooth muscle.

74. An investigation into the maximum activities of four key enzymes in the muscle of malnourished patients with cancer or benign disease

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There is a depression of key enzymes controlling glucose and glycogen breakdown in the muscle of malnourished patients with cancer (Lundholm et al., 1978). It has been suggested that this is due to a specific action of the tumour but it is not known if it also occurs in malnourished patients without cancer.

We have studied the maximum activities (MA) of four key enzymes of glucose oxidation in skeletal muscle obtained from 11 patients with cancer (mean age 68±3·3 years and mean weight loss 15·8±2·0 per cent) and from 10 with benign disease (mean age 59±4·9 years and mean weight loss 19·9±2·3 per cent). In small samples of rectus muscle, measurements were made of α-ketoglutarate dehydrogenase (α kg) an an indicator of the MA of the Krebs cycle, phosphofructokinase (PFK) for glycolysis, fructose 1·6-diphosphatase (F16DP) for substrate cycling in the fructose 6 phosphate-fructose 1·6-diphosphate couple and hexokinase (HK) as an indicator of the MA at which glucose can be channelled into hexosephosphates of the glycolytic pathway.

	HK*	PFK*	F16DP*	α kg*
Cancer	0·89±0·23	29·8±1·72	0·61±0·12	0·10±0·03
Benign disease	1·14±0·13	30·9±2·6	0·78±0·2	0·09±0·02
P	n.s.	n.s.	n.s.	n.s.

All results expressed as mean±s.e. mean.

*MA as μmol min⁻¹ g muscle⁻¹.

These results show that the MA of Krebs cycle, glycolysis, glucose mobilization and the sensitivity to glucose utilization by the substrate cycle PFK/F16DP is similar in both patient groups. The steady-state levels of the enzymes we have measured are less than published control values and are more likely to be the consequence of malnutrition rather than a specific action of the tumour.

LUNDHOLM K., EDSTROM S., EKMAN L. et al. (1978) A comparative study of the influence of malignant tumour on host metabolism in mice and man. *Cancer* **42**, 453–461.

75. Reduction of operative morbidity and mortality by combined preoperative and postoperative nutritional support

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Reduction of operative morbidity and mortality by preoperative nutritional support (TPN) has never been adequately demonstrated. To determine if preoperative nutritional assessment can identify patients at increased risk of subsequent nutritionally based complications, and to determine if preoperative TPN decreases morbidity and mortality in this high-risk group, 306 elective surgical patients underwent nutritional assessment on admission including albumin (ALB), transferrin (TFN), total protein, mid-arm muscle circumference, triceps skinfold (TSF), lymphocyte count, delayed hypersensitivity reactivity (DH), weight and weight loss history. The patient's clinical course was monitored until death or discharge. Based on the first 161 patients, computerized discriminant analysis identified parameters predicting morbidity and mortality and a linear predictive model was developed.

Predicted risk (%) = 158−16·6 (ALB)−0·78 (TSF)−0·2 (TFN)−5·8 (DH).

To test for predictive accuracy and clinical applicability, and to determine the efficacy of TPN in decreasing morbidity and mortality in the high risk group, the model was applied prospectively to two groups of patients undergoing major elective surgery to permit comparison of actual and predicted outcome (group 1, patients receiving no preoperative TPN; gruop 2, patients receiving pre- and postoperative TPN).

	Low (<40%)	Int. (40–49)	High (>49)	*P*< (χ^2)	*P*< high risk†
Actual outcome (% of patients/group)					
No.					
No. TPN	32	18	25	—	—
TPN	18	10	22	—	—
Complications					
No. TPN	13	44	56	0·001	0·01
TPN	11	20	23	0·001	
Sepsis					
No. TPN	9	17	36	0·01	n.s.
TPN	6	20	14	n.s.	
Major sepsis					
No. TPN	6	17	33	0·01	0·05
TPN	6	0	5	n.s.	
Death					
No. TPN	6	22	47	0·001	0·01
TPN	0	0	9	n.s.	

† TPN *v*. No. TPN.

The first step in rational nutritional management is nutritional assessment to identify the high risk patient. This clinically applicable model provides an index of nutritional status which accurately and prospectively identifies patients at increased risk of operative morbidity and mortality. In this high risk group, combined with pre- and postoperative nutritional support reduces operative morbidity ($P<0·01$) and mortality ($P<0·01$).

76. Metabolic homeostasis during liver transplantation in the pig

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Hepatectomy followed by orthotopic liver transplantation in the pig has been used in the present work as an experimental model to study the role of the liver in the control of metabolic homeostasis.

Ten 24-h fasted pigs were totally hepatectomized and homologous livers from 24-h fasted donors were transplanted orthotopically with a preservation time of less than 60 min. Sham operated animals were used as controls. Liver biopsies were rapidly placed in liquid nitrogen for glycogen analysis and blood samples were collected from the external jugular vein at different times during the operation. Glucose and glycerol were evaluated in plasma by enzymatic methods, free-fatty acids by a colorimetric method and individual amino acids by using a 121-MP Beckman autoanalyser with nor-leucine as internal standard.

Glycogen concentration decreased in the donor's liver during the preservation period and after the transplant. Plasma levels of glucose, alanine, ornithine, taurine, glycerol and free fatty acids increase while the levels of glutamate decrease and those of arginine completely disappear during the 'ahepatic phase'. Up to the thirtieth minute after the end-to-end portal anastomosis, blood glucose levels were decreased compared with controls, while the values of glycerol, free fatty acids and glutamate were normal, the other amino acids being maintained at the same level as during the 'ahepatic phase'.

The glucose production from extrahepatic organs supported by the release of amino acids from the muscles and the utilization of lipid stores maintain glucose homeostasis during the 'ahepatic phase'. The length of time the transplanted liver takes to get over its biosynthetic activity in the presence of its rapid consumption of metabolic fuels endangers the survival of the animal and indicates exogenous perfusion of substrates.

77. Studies of peritoneal phagocytes as therapy for faecal peritonitis

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Peritonitis remains a leading cause of postoperative death despite operation and antibiotics. Interest in natural defences led to this study of intraperitoneal phagocytes (Pph) as specific therapy for established bacterial peritonitis.

Peritoneal phagocytes were harvested from Sprague–Dawley rats 72 h after stimulation with i.p. zymosan. Viable cells were subjected to differential counting and phagocytic activity assessed by chemiluminescence. Pph in a ratio of 10 cells/bacterium were injected i.p. in rats 2 h after an LD_{90} i.p. dose of sterile human faeces and *Escherichia coli*. Controls received equal volumes of saline i.p. *In vitro* studies of bacterial inactivation by Pph were also performed. Pph (10^7 cells) were incubated for 4 h with 10^8 *E. coli* in each of four solutions: (A) Pph+*E. coli*+saline; (B) Pph+*E. coli*+2 per cent haemoglobin (HGB); (C) Pph+*E. coli*+sterile faeces; (D) Pph+*E. coli*+peritoneal exudate. Because HGB is an inhibitor of phagocytosis, solution B was used as an *in vitro* model of impaired bacterial inactivation. Solution C was prepared from autoclaved faeces. Solution D was a cell and bacteria-free filtrate of peritoneal fluid from rats dying of peritonitis. Twenty-four hour mortality rates were recorded for *in vivo* studies. Quantitative cultures obtained before and after incubation allowed expression of bacterial inactivation *in vitro* as a percentage of original concentration.

$$\left(1-\frac{\text{Org/ml after incubation}}{\text{Org/ml before incubation}}\times 100\right).$$

Eleven of 12 (92 per cent) control rats died as did 10 of 12 treated rats (83 per cent). *In vitro* inactivation data are shown:

	% inactivation			
Solution	A	B	C	D
2 h	60	60	0*	0*
4 h	90	60	0*	0*

*$P = 0·05$ compared to solution A.

Factors are present in sterile faeces and filtered peritoneal exudate which prevent bacterial inactivation by Pph, and apparently preclude improved survival by this method.

78. Can intravenous fat emulsions be justified as a non-protein calorie source?—a controlled clinical trial

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The cost per calorie of intravenous fat is 10–20 times greater than hypertonic dextrose. The advantages of fat emulsions must therefore be unequivocal before their routine use as a non-protein calorie source (NPCS) can be recommended.

We have studied 22 critically ill surgical patients who required intravenous nutrition (IVN). They were matched for age, sex, pre-illness weight, weight loss and diagnosis and allocated to two treatment groups: group 1 (6F, 5M; 60±14 years) received 50 per cent dextrose as the NPCS (mean calorie intake; 50±9 kcal kg^{-1} d^{-1}) and group 2 (7F, 4M; 61±19 years) 60 per cent of their NPCS as fat and 40 per cent as dextrose (56±11 kcal kg^{-1} d^{-1}). Both groups received an 8·5 per cent crystalline amino acid solution providing a calorie to nitrogen ratio of 150 : 1. The changes in body weight, fat, protein and water over the 2 week study period were calculated by the method of Hill et al. (1978). Plasma proteins and liver function tests were also measured.

The results for the groups were as follows:

	Group 1	Group 2
ΔWeight (kg)	2·2±0·8*	2·4±0·7**
ΔFat (kg)	0·9±0·3*	0·3±0·3
ΔProtein (kg)	0·1±0·3	0·3±0·2
ΔWater (kg)	1·3±0·9	1·7±0·7*
ΔAlbumin (gl/)	−0·45±0·4	1·1±0·3
ΔGOT (i.u./l)	13·1±2·3	2·8±1·1

All results expressed as mean±s.e. mean.

* Significant at 5 per cent level by paired *t* test.

** Significant at 1 per cent level.

None of the changes in group 1 is significantly different from those in group 2 (non-paired *t* test) except the plasma GOT ($P<0·01$) where the magnitude of the change is unlikely to be of clinical importance. We conclude that the routine use of fat emulsions as a NPCS is not justified on the basis of cost.

HILL G. L., MCCARTHY I. D., COLLINS J. P. et al. (1978) A new method for the rapid measurement of body composition in critically ill surgical patients. *Br. J. Surg.* 64, 723–735.

79. Tissue perfusion in extracorporeal circulation using bubble or membrane oxygenators

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Improvements in blood compatibility and microcirculation have been claimed by using membrane oxygenators (MO) instead of bubble oxygenators (BO) in open heart surgery. These mainly clinical impressions have not been substantiated, with regard to tissue perfusion. Using Po_2 histograms muscle perfusion in dogs undergoing ECC (2 h) was studied with BO ($n=8$) or MO ($n=7$). Po_2 was measured with a P_2-multiwire ($n=8$) surface electrode. The frequency distribution of 104 Po_2 values was recorded and graphically plotted by a computer program which represents one histogram. These histograms were measured before operation (H_1), after cannulation for total bypass was performed (H_2), immediately after partial bypass (H_3), during 1 hour's (H_4) and 2 hours' (H_5) perfusion and 1 h after perfusion (H_6).

Haematological studies including platelet numbers and function (ADP-induced aggregation) were performed. The circuit was primed with about 1·0 l of homologous blood. After precirculation (10 min) of the dog (400 ml/min) an initial fall in platelet numbers and function was measured and this coincided with a severe impairment of H_3 while arterial pressures frequently showed an initial rise often followed by a severe pressure drop. The continuously monitored muscle surface Po_2 dropped to zero. A severe shunting phenomenon is apparently the initial reaction following the first blood contact with foreign material. During perfusion the histograms (H_4 and H_5) remained acceptable in both groups and were mainly dependent on the perfusion pressures. After ECC a clear differentiation appeared between the BO and the MO groups. In the BO group severely impaired histograms (H_6) were observed correlating with higher systemic vascular resistance (SVR) and decreased platelet numbers and function. In contrast, the MO group had normal histograms (H_6), low SVR and better maintained platelet numbers and function.

In this study improvements of MO compared to BO could be quantitated in regard to better tissue perfusion after ECC which correlated with a better haemocompatibility. Po_2 muscle surface histograms appeared to be a reliable method to evaluate tissue perfusion objectively and substantiate the clinical observation that patients after MO perfusion have a better peripheral circulation than patients after BO perfusion.

80. Induction of pulmonary dysfunction by fragment D: platelet aggregation

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The plasma concentration of fibrinogen degradation product D (FDP-D) is markedly increased following burn or trauma. Purified human FDP-D infused into awake, restrained, untraumatized rabbits (100 μg/ml blood) causes progressive thrombocytopenia, pulmonary dysfunction, vascular leak and interstitial neutrophilia (Luterman et al., 1977). Rabbits treated with diphenhydramine (Benadryl) prior to FDP-D infusion fail to develop this pathology (Mainwaring et al., 1978).

This study examined platelet aggregation, ATP release and prostaglandin synthesis in rabbits receiving FDP-D (group 1, $n=4$) alone or FDP-D following diphenhydramine pretreatment (group 2, $n=4$). Platelet-rich plasma (PRP) was prepared from citrated blood drawn via a femoral arterial catheter at 0, 1, 2½ and 4 h post infusion. Platelet aggregation was stimulated with either collagen or ADP. Malonaldehyde (MDA), a byproduct of prostaglandin synthesis, was measured by colorimetry. Animals were sacrificed at 4 h.

	Group 1		Group 2	
	0 h	4 h	0 h	4 h
Agg. (% T)	57·5±6·0	70·5±4·5	44·5±13·2	49·3±15·8
Time (min)	3·7±0·28	1·6±0·44*	3·1±0·24	3·6±0·71
Lag (min)	0·7±0 12	0·1±0 07*	0·9±0·12	0·8±0·33
Shape change (min)	0·8±0·24	0·1±0·07**	1·2±0 45	1·4±0·55
μMATP	34 8±7·9	64·5±11·5†	29·0±8·7	19·7±6·9
min	3·1±0·12	1·5±0·30††	2·9±0·12	2·2±0·17
nmol MDA	0·07±0·03	0·09±0·04	0 08±0·03	0·02±0·01

Response to 0·5 μg collagen, $\bar{x}$±s.e. mean.
* $P<0\ 005$; ** $P<0·01$; † $P<0·05$; †† $<0·002$; change from time 0.

Aggregation and release were enhanced in FDP-D PRP since all response times shortened. Total ATP and MDA release increased. Diphenhydramine pretreatment inhibited FDP-D simulated aggregation, ATP release and prostaglandin synthesis. No pretreated animal had thrombocytopenia or respiratory distress. Enhancement of platelet aggregation and release represents one mechanism by which FDP-D induces pulmonary dysfunction. Diphenhydramine inhibits these responses and may prove therapeutic in post-traumatic pulmonary complications.

LUTERMAN A., MAINWARING D. and CURRERI P. W. (1977) The role of fibrinogen degradation products in the pathogenesis of the respiratory distress syndrome. *Surgery* 82, 703–709.

MAINWARING D. THORNING D. and CURRERI P. W. (1978) Mechanisms of acute pulmonary dysfunction induced by FDP-D. *Surgery* 84, 45–54.

81. Clinical comparison of haemostasis in membrane and bubble oxygenator perfusion

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Most clinical evaluations of bubble oxygenators (BO) compared to membrane oxygenators (MO) report no or only minor differences in postoperative blood transfusion requirements. However, other facts like cardiotomy suction might obscure important differences, especially when no sensitive indices like platelet function are measured.

In this clinical study of 40 strictly comparable coronary artery bypass operations the Travenol TMO was used in 21 patients and the Polystan VT 5000 in 19 patients. In the TMO group platelet function was better maintained (>35 per cent) as compared to the VT group during the period of aortic crossclamping, but decreased rapidly when intensive cardiotomy suction started. After protamine administration a further impairment of platelet function was seen. Consequently, after perfusion the functions in the TMO group were the same as the VT group, which was already impaired shortly after the onset of perfusion. During the VT perfusion platelet numbers were more affected ($P<0·02$) compared to the numbers during TMO perfusion. There were no significant differences in erythrocyte number, plasma haemoglobin, postoperative blood loss or blood transfusion requirements in the two groups.

In conclusion, no difference in haemostasis could be measured after BO and MO perfusion. However, the haematological data during perfusion showed that improvements by TMO perfusion were obtained, but were counteracted by cardiotomy suction and protamine administration. After perfusion equal levels of platelet numbers and function were measured in both groups which substantiate the common finding of equal haemostasis in BO and MO perfusion. Improvements in haemostasis with MO perfusion are only to be expected when the damage by suction and protamine administration can be controlled.

82. The effect of ischaemic arrest on the compliance of the canine left ventricle measured by changes in regional passive elastic stiffness

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Detection of changes in left ventricle (LV) compliance may prevent irreversible ischaemic injury during cardiac surgery.

We developed a gauge to measure passive elastic stiffness (PES) of myocardium in intact, arrested left ventricles (LV). A miniature hydraulic system stretched a segment of myocardium up to 140 per cent of initial length while recording the pressure developed within the system. Serial force-length (FL) curves were recorded for 15 excised LV during the onset of rigor.

Myocardial PES was measured for the left ventricular free wall and for the interventricular septum in two orientations—parallel to (longitudinal) and perpendicular to (circumferential) the long axis of the LV. Serial pressure-volume (PV) curves were recorded as an index of global compliance.

Exponential curves were fitted to the digitized FL and PV curves by computer. Analysis of variance revealed no significant difference in PES between free wall and septum. Percentage extension produced by a given force decreased as a function of time on both orientations, paralleling the changes in the PV curves ($P<0·001$). Although there was no significant difference between longitudinal and circumferential PES measured initially ($P<0·5$), longitudinal was significantly greater than circumferential PES at rigor ($P<0·001$).

We conclude that changes in regional PES of myocardium can be used to monitor ischaemic changes in global LV compliance.

83. Surgical application of an artificial pancreas

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The artificial pancreas (AP)—insulin and glucose administration under computer control—has usually been applied in the medical emergency (e.g. diabetic coma) and in order to establish the insulin requirement of unstable diabetic patients. We present two new applications of the AP to surgical patients.

Hyperinsulinism: Continuous recording of blood glucose level during a fasting period is an established procedure in the diagnosis of insulinoma. With AP this information can be quantified by the determination of the amount of glucose needed to maintain a normal glucose level and thus performing the test without the risks inherent to hypoglycaemia. In a 30-year-old male, AP was connected before and during surgical removal of a pancreatic tumour and it reduced within minutes of removal of the tumour the need for exogenous glucose, clearly indicating that only one insulinoma was involved and had been removed. The artificial pancreas was also connected to a 10-month-old girl who had suffered from birth frequent attacks of severe hypoglycaemia. These symptoms were attributed to nesidioblastosis, a diffuse hyperplasia and ectopic localization within the pancreas of the endocrine tissue. This girl required continuous glucose administration (3–6 g/h) to maintain normoglycaemia. A 75 per cent pancreatectomy was performed with no reduction in the amount of glucose administered over the next 24 h (3·3±0·1 g/h). A second operation was then performed leading to a 90 per cent pancreatectomy. Exogenous glucose was no longer needed and 3 months later the child maintains normoglycaemia. The diagnosis of nesidioblastosis was confirmed histologically.

Total parenteral nutrition: AP was applied to total parenteral nutrition in 7 totally or partially pancreatectomized patients mainly during and after acute episodes of sepsis. When these patients were connected to the AP the blood glucose level was maintained strictly in the normal range even with increasing administration of glucose.

In conclusion, AP has been found to be a reliable method of maintaining normoglycaemia over prolonged periods with minimal medical supervision.

84. A simplified procedure of canine pancreatic tissue preparation for intrasplenic autotransplantation

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Under pentobarbital anaesthesia and aseptic conditions, the horizontal part of a dog pancreas was removed, its volume measured and subsequently placed in a Petri dish and infiltrated with a solution of collagenase (2000 U/ml; type 1 Sigma Chemical Co., St Louis, Mo.). Three ml of this solution were employed to infiltrate 1 ml of pancreatic tissue. After complete infiltration, the swollen gland was cut by hand with a scalpel in the same Petri dish into 2–4 mm particles. The entire contents of the Petri dish were then carefully transferred into a beaker and rinsed with 1 l of Ringer's lactate solution pre-heated to 37 °C (1 mM $NaHCO_3$ added to raise pH to 7·50). The contents of the beaker were allowed to sediment for 5 min. The supernatant was removed and additional rinsing and sedimentation were performed, after which the sedimented tissue was transferred to a syringe and autotransplanted into the animal's spleen. The surgical procedure was terminated with the removal of the remaining pancreatic tissue. Postoperatively, the dog received no antidiabetic treatment. Of the 14 dogs so studied, 13 animals became spontaneously normoglycaemic; this normoglycaemia persisted for many months and in one case, up to 2 years. Postoperative glucose-loading tests gave values that were not significantly different when compared with those obtained from control animals. Concurrently, plasma insulin levels rose promptly to values not significantly lower than in non-operated dogs. Histological examination of the spleens of normoglycaemic animals confirmed the existence of multiple foci of endocrine and exocrine tissue of normal appearance.

85. Function of an ectopic liver recomposed from transplanted hepatocytes in the spleen

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Based on the similarity displayed by transplanted isolated hepatocytes in the spleen with normal hepatic architecture, an ectopic liver was examined for biological functions.

Twenty inbred adult Wistar rats in which isolated hepatocytes were transplanted in their spleens 1 year previously were used.

1. Histochemical (periodic acid-Schiff and G-6-Pase stains) and immunofluorescent (albumin) studies and α-fetoprotein (AFP) measurements were performed.

2. Six out of 20 rats underwent portacaval shunt (PC shunt) and subsequently, at 3–4 weeks, Indocyanine Green (ICG) clearance (0·5 mg/100 g BW) and ammonia tolerance (0·05 ml of 2·14 per cent NH_ACl/100 g BW) tests were done. In the ammonia tolerance test, the hepatic artery was ligated immediately after NH_4Cl injection in order to detect the isolated function of the ectopic liver from the host liver. Six normal rats with PC shunt but without transplantation were taken as a control.

1. Periodic acid-Schiff stain revealed generous glycogen granules in the cytoplasm of transplanted hepatocytes and G-6-Pase stain specifically demonstrated cellular viability.

2. Immunofluorescent study clearly demonstrated that the transplanted hepatocytes synthesized the albumin.

3. No detectable AFP was measured in sera.

4. ICG clearance test: half-life in the blood of rats with an ectopic liver was 5·92±0·92 min when compared with 7·37±0·31 min in control rats. The difference was statistically significant ($P<0·05$).

5. Ammonia tolerance test: the blood ammonia concentration immediately after the injection was lowered to a mean of 94·7 per cent of the initial value 15 min after the injection in rats with an ectopic liver. In control rats without an ectopic liver, it showed a mean of 28·7 per cent of the initial value.

An ectopic liver recomposed from isolated hepatocytes transplanted in the spleen of syngeneic rats for 1 year had the biological potential to synthesize albumin and glycogen. The differences between rats with and without an ectopic liver in Indocyanine Green clearance and ammonia tolerance tests can be evaluated as reflecting a functioning ectopic liver in the spleen.

86. Correlation of speech with tongue mobility and area resected after surgery

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Fixation of the tongue and loss of mobility are said to interfere with articulation (Summers, 1974). Little information is available on the amount of tongue that can be removed before speech is seriously impaired.

Speech was measured by articulation scores of phonemes (Bradley et al., 1979). Forty-four patients who had undergone surgery to their tongue were studied.

Four parameters of mobility were measured: protrusion and lateral deviation of the tip of the tongue and elevation of the centre and base of the tongue.

The area of the tongue was assessed by measuring tongues taken at post mortem. Using this 'average' tongue the area of tongue remaining in the above 40 patients was measured as a fifth variable.

Multiple linear regression of the articulatory score against the above five predictor variables showed significant overall regression ($r=0·79$, $F_{5,34}=11·54$, $P<0·001$), but of the five variables only the area resected was significant ($t_{34}=2·82$, $P<0·01$).

The data were then reanalysed by linear regression in two groups—those with and those without replacement of the tongue by distant flaps. There was no statistical difference between the two slopes. The entire data were then combined giving the result: $\log_{10}$ articulatory score = 1·76 − 0·015 area resected.

From this it can be calculated that the articulatory score remains within intelligible limits until 24 per cent of the tongue has been resected. Replacement of bulk by a distant flap does not appear to improve articulation.

BRADLEY P. J., HOOVER L. and STELL P. M. (1979) Objective assessment of speech after surgery to the tongue. *Clin. Otolaryngol.* (In the press.)

SUMMERS G. W. (1974) Physiological problems following ablative surgery of the head and neck. *Otolaryngol. Clin. North Am.* **1**, 217–250.

87. Electrical sizing of cultured glial and nerve cells: a novel method for measurement of cell swelling

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Cell swelling is a basic phenomenon in many kinds of tissue damage. Cytotoxic swelling of glial and nerve cell elements is an important component in brain oedema of various origins. However, no information is available so far, leading to an understanding of the mechanisms involved which would be necessary to develop specific therapeutic concepts. Progress in culture techniques of nerve cells and the availability of defined glial and nerve cell lines makes it possible to approach this problem experimentally. Volume measurements of single cells suspended in a medium can be accomplished with considerable precision. This laboratory employs an advanced cell sizing method (Metricell) which is based on the Coulter principle. A particle passing through a Coulter aperture impedes a current flowing through the same orifice. The change in voltage (pulse) produced by the particle is in proportion to the particle cross-section, and hence volume. Considering further parameters, (*a*) the applied current, (*b*) conductivity of the medium, (*c*) shape and resistance of the cell, (*d*) geometry of the aperture, cell volume can be directly computed employing a modified Maxwell equation.

The measuring system is fully computerized providing impulse-height analysis, online data storage and calibration, display of the current measuring process on a terminal and calculation of the mean cell volume and standard deviation. All pertinent data of an experiment are stored together with the complete volume histogram.

Swelling experiments of glial and nerve cells harvested after cultivation are conducted in a temperature controlled chamber. The chamber is persufflated with O_2, CO_2 and N_2 mixtures of any concentration desired. Po_2 and pH can be continuously monitored. Any condition suspected to prevail in the extracellular compartment in brain tissue after mechanical damage, ischaemia or severe general metabolic derangements can be mimicked in the chamber, such as acidosis, hypoxia, high K^+ concentrations, hypo- or hyperosmolarity, in order to study the cellular swelling response. Determinations of intra- and extracellular concentrations of relevant metabolites and ions permit evaluation of membrane permeability changes and of underlying biochemical processes.

88. Is general anaesthesia really the cause of postoperative chest complications? A controlled trial of three methods of anaesthesia for herniorrhaphy

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In an attempt to assess the respiratory effects of general anaesthesia as opposed to those of an incision through the abdominal parietes, we used a standard method of inguinal herniorrhaphy and randomized the type of anaesthetic.

Eighty-six patients were randomly allocated to general (GA), epidural (EA) or local infiltration anaesthesia (LA). Respiratory function was tested by spirometry (FEV_1 and FVC) and estimation of PaO_2 before and 4 h and 24 h after operation.

In the GA group 59 per cent of the patients had a 4 h FEV_1 <80 per cent of their preoperative figure, compared with 33 per cent of those after LA ($\chi^2=3{\cdot}85$, $P<0{\cdot}05$). The corresponding figures at 24 h were 41 per cent and 10 per cent ($\chi^2=7{\cdot}25$, $P<0{\cdot}01$). After EA 48 per cent of patients at 4 h and 46 per cent at 24 h had FEV_1 <80 per cent of their preoperative level, but the figures were significantly different from the LA group only at 24 h ($\chi^2=9{\cdot}28$, $P<0{\cdot}01$).

FVC was more often depressed after GA than after either EA or LA but the differences were not significant. Pao_2 did not deviate significantly from preoperative readings in any of the groups.

We conclude that general anaesthesia does play a part in the respiratory depression after abdominal operations.

89. Autotransplantation of small intestine to replace the thoracic oesophagus in adult dogs and puppies: an experimental study with 1-year follow-up

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The technique to reconstruct a defect in the oesophagus by autotransplantation of intestinal segments as reported first by Seidenberg in 1959 has been used only in the cervical region.

The aim of this experimental study was first to investigate the applicability of this technique in a modified form for bridging a gap in the thoracic oesophagus and secondly to evaluate this procedure in small fast-growing individuals. A follow-up period of 1 year was planned. The first part of the experiment consisted of a group of 20 young adult beagles, mean weight 11·6 kg. In the second part the operation was carried out on 11 mongrel puppies, 8–12 weeks old, mean weight 9·3 kg.

In all cases an ileal segment was used. This required a 10–30 per cent resection of the total small bowel length. The mesenteric artery was anastomosed end-to-end to the internal mammary artery with a continuous 7/0 silk suture in the adult dogs and with an interrupted 7/0 silk suture in the puppies. The mesenteric vein was anastomosed to the superior caval vein with a continuous 7/0 silk suture in all cases. Four to six cm of the mid-thoracic oesophagus were resected and replaced by an ileal segment of equal length. All oesophago-ileal anastomoses were performed with a two-layer chromic catgut suture.

In the adult group 7 dogs and in the puppy group 4 dogs died. In each group 1 dog died of untreated shock and 6 adult dogs and 3 puppies of necrosis of the transplant by vascular thrombosis.

The remaining 20 dogs, 13 adults and 7 puppies, were followed-up. In one adult dog after total necrosis of the transplant a stricture was found. In the other 19 dogs (12 and 7) vascular patency was confirmed by angiography. Repeated oesophagoscopies showed no stricture and normal peristalsis of the transplant could be observed in all cases. Radiography at regular intervals showed good passage of contrast except in 2 puppies. In both cases a functional stenosis of the transplant was seen with enormous dilatation of the proximal oesophagus. As a result of this complication 1 was sacrificed at 19 weeks.

The adult dogs could eat adequately, kept their operation weight and were clinically in good shape. Five puppies could eat adequately and reached their estimated adult weight 3–6 months after operation with a weight-gain of 33–125 per cent. One puppy, with functional stenosis, needed special care to maintain his body weight slightly above the operation weight.

All dogs were sacrificed 1 year after the operation.

Post-mortem angiography showed extensive transanastomotic circulation at the oesophago-ileal connections.

Histological studies showed that the structure of the oesophageal wall and ileal wall was normal.

90. The cytological diagnosis of thyroid swellings

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Despite its unpopularity with British surgeons, fine needle aspiration biopsy of the thyroid is a simple technique offering precise identification of goitres (Bain and Crockford, 1978). Several comprehensive reports attest its reliability (Einhorn and Franzén, 1962). For 12 years this technique has been evaluated in surgical practice. Basic thyroid cytology was learned from imprint smears of 54 varied thyroidectomy specimens. Thereafter fine needle biopsy and cytological examination was included with conventional thyroid investigations in the diagnosis of 204 goitres, 128 of which were confirmed histologically. The entire series was carefully followed up.

There were no technical failures and minimal complications. All 36 cases of histologically confirmed neoplasm had been detected by preoperative cytological study, while benign follicular adenoma (8 cases) was successfully differentiated from carcinoma (25) and non-Hodgkin's lymphoma (3). Cytology correctly predicted the histological type in 26 of 28 malignant goitres. Among 168 non-neoplastic swellings, the cytodiagnostic features of nodular (115 cases) or toxic (11) goitre and of Hashimoto's (28) or de Quervain's thyroiditis (4) were clearly recognized on the aspirate smear, thus frequently avoiding surgical intervention.

Since many thyroid cancers present as goitres that feel benign, accurate clinical evaluation must remain difficult even in experienced hands. Fine needle aspiration biopsy of the thyroid is reliable and safe and provides valuable diagnostic information.

BAIN G. O. and CROCKFORD P. M. (1978) Invited commentary on needle aspiration and needle biopsy of the thyroid. *World J. Surg.* **2**, 324–326.

EINHORN J. and FRANZÉN S. (1962) Thin needle biopsy in the diagnosis of thyroid disease. *Acta Radiol.* **58**, 321–336.

91. Acute stress ulcer: an experimental study

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Acute stress ulcer is one of the most troublesome problems for surgeons because of its sudden onset, massive haemorrhage, poor risks due to background condition and low operative success.

This paper presents an experimental study of pathophysiology from the viewpoint of secretion and prevention using (synthetic) gastric inhibitory polypeptides.

A total of 400 rats weighing approximately 200 g each was given restraint ulcers and divided into four groups: (*a*) control group, (*b*) surgically vagotomized group, (*c*) medically vagotomized group, (*d*) gastric inhibitory polypeptide (synthetic GIP, synthetic neurotensin and synthetic somatostatin) infused group. The stomachs were examined by light and electron microscopy.

In the control group (*a*) approximately 85 per cent of the rats showed gastric bleeding and erosion. In the surgically vagotomized group (*b*) only 10 per cent showed ulcer formation. In the medically vagotomized group (*c*) (atropine and hexamethonium bromide) there was no ulcer formation. In the group infused with gastric inhibitory polypeptides (*d*) there was little or no ulcer formation (GIP 40 per cent, somatostatin 0 per cent).

In stomachs with ulcers both exocrine cells (parietal and chief cells) and endocrine cells (G cells and EC cells) showed evidence of hyperfunction by electron microscopy; in the ulcer-prevented groups these cells were in a state of hypofunction.

These findings indicate that continuous intravenous infusion of synthetic somatostatin will be effective in the prevention of stress ulcers in poor risk patients.

92. The distribution and density of apocrine glands in hidradenitis suppurativea

W. P. MORGAN and L. E. HUGHES, *University Department of Surgery, Welsh National School of Medicine, Cardiff* (*see* pp. 853–856)

93. Continent anal ileostomy with mucosal proctectomy: a bloodless technique using a surgical ultrasonic aspirator in dogs

W. J. B. HODGSON, J. L. FINKELSTEIN, PHILLIPA WOODRIFFE and A. AUFSES JUN., *Surgical Service, Veterans Administration Medical Center, New York, USA* (*see* pp. 857–860)

94. Oral mannitol for mechanical bowel preparation

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Conventional mechanical bowel preparation with enemas and purgatives is not always effective and takes 3–5 days. Whole bowel irrigation (WBI) with normal saline delivered through a nasogastric tube is rapid and efficient, but unpleasant to the patient and associated with sodium and water retention (Crapp et al., 1975). Oral mannitol may reduce the electrolyte disturbances of whole bowel irrigation (Donovan et al., 1978).

We have developed a method of oral bowel preparation with mannitol and water (group A) which avoids a nasogastric tube. Results have been compared with patients having WBI with mannitol (group B) or WBI alone (group C). In group A ($n = 20$) preparation was successful in all except four patients, 2 with a small lumen diameter (<5 mm). In group B ($n = 21$) preparation was successful in all but 2 patients who vomited. In group C ($n = 20$) 6 patients had inadequate bowel preparation. The mean duration of preparation was 3·9 h for group A, 3·4 h for group B and 4·5 h for group C. The mean fluid gain was 305 ml for group A, 1160 ml for group B and 2700 ml for group C. The mean sodium gain was 200 mmol for group A, 324 mmol for group B and 564 mmol in group C.

These results indicate that oral mannitol is effective and is more acceptable to patients than WBI and avoids the problem of fluid and sodium retention.

CRAPP A. R., TILLOTSON P., POWIS S. J. et al. (1975) Preparation of the bowel by whole gut irrigation. *Lancet* **2**, 1239–1240.

DONOVAN I. A., ARABI Y., KEIGHLEY M. R. B. et al. (1978) Modification of the physiological disturbances produced by whole gut irrigation by preliminary mannitol administration. *Br. J. Surg.* **65**, 827.

95. Gastrointestinal adaptation in patients with ileostomy

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Patients are said to adapt to the loss of the colon by reducing the volume of the ileostomy effluent. One possible mechanism for this 'adaptation' is a reduction in gastrointestinal transit, allowing more time for absorption.

We have studied gastric emptying and intestinal transit times in patients with established ileostomy using ^{99}Tc-labelled bran as a marker of transit of food. Bran is an ideal vehicle, being a natural dietary residue, and our *in vivo* and *in vitro* studies show that the bran–technetium bond is stable in gastrointestinal secretions.

Gastric emptying was measured using the gamma camera method in 30 patients (15 with ileostomy and 15 normal controls) after ingestion of a marker incorporated into a meal. The mean rate of gastric emptying was 0·74 per cent per minute in ileostomy patients, not significantly different from 0·84 per cent per minute in normal controls. Gastric residue at 90 min was 38 per cent of the meal in ileostomy patients compared to 25 per cent in the normals.

Mouth to stoma transit times were compared with mouth to caecum transit times in controls. In 8 out of the 10 controls, the peak transit time (mouth to caecum) was 4 h or less; however, in all the ileostomy patients ($n = 15$) the peak transit time lay between 4 and 8 h ($P < 0{\cdot}001$ χ^2 with Yates' correction).

Our data supports the hypothesis that there is a delay in gastrointestinal transit in patients with established ileostomies. This delay allows increased time for absorption of fluid and electrolytes.

96. Natural history of perianal Crohn's disease

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Perianal disease is a frequent presentation of regional enteritis but in our experience these lesions often remain quiescent for many years.

The aim of this study has been to examine the natural history of perianal Crohn's disease from a 10-year follow-up of 109 patients with histological Crohn's disease and anal lesions. Fourteen patients (13 per cent) have died from unrelated disorders. Ten have acquired excision of the rectum but only 5 for perianal disease (4·5 per cent). Of the remaining 85 patients, 61 have been followed up by proctoscopy and rectal biopsy. Anal tags were still evident in 25 of 37 patients (68 per cent) but new tags had appeared in 2 patients. Only 10 of 53 fissures (19 per cent) were still present at 10 years and there were no new fissures. Fistulas were still present in 7 of 21 subjects (33 per cent) but were asymptomatic, the remainder had healed spontaneously ($n = 8$) or following operation ($n = 6$) and new fistulas had appeared in only 5 patients. The one patient with a stricture still has a stricture, but anal stenosis has developed in 29 patients, 27 of whom had had a fissure. None of the patients have become incontinent.

These results indicate that perianal manifestations of Crohn's disease pursue a relatively benign course and are rarely an indication for proctectomy.

97. Effect of 5-fluorouracil [5FU] on pancreatic protein secretion: its rationale in the treatment of acute experimental pancreatitis

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It has been postulated (Knight and Condon, 1971) that drugs which inhibit protein synthesis might be useful in the treatment of acute pancreatitis. Three studies are described in which an attempt was made to investigate the action of the chemotherapeutic drug 5FU in this context.

1. Effect on pancreatic protein secretion: in six experiments using the isolated perfused canine pancreas (Hermon-Taylor, 1968), it was found that 5FU significantly inhibited total pancreatic enzyme output ($P<0{\cdot}01$).

2. Effect on pancreatic protein secretion coupling: as cyclic GMP has been postulated to control release of zymogen granules containing exportable proteins (Albano, 1976) an attempt was made to determine the effect of 5FU on cyclic GMP and zymogen granule discharge in guinea-pig pancreatic lobules. In six experiments 5FU significantly reduced tissue levels of cyclic GMP ($P<0{\cdot}01$) and inhibited release of zymogen granules ($P<0{\cdot}01$).

3. Effect on acute experimental pancreatitis: 10 guinea-pigs with a Pfeffer loop showed histological evidence of acute pancreatitis within 12 h.

In 10 guinea-pigs 25 mg of 5FU were given i.v. 3 h after the loop was created. At 12 h there was no histological evidence of acute pancreatitis.

From these studies it would appear that 5FU could prove to be of value in the treatment of developing acute pancreatitis.

ALBANO J. K. (1976) Intracellular messenger role of cyclic GMP in exocrine pancreas. *Nature* **261**, 404–406.

HERMON-TAYLOR J. (1968) A technique for perfusion of the isolated canine pancreas. *Gastroenterology* **55**, 488–501.

KNIGHT M. J. and CONDON J. R. (1971) Possible use of glucagon in the treatment of acute pancreatitis. *Br. Med. J.* **2**, 440–442.

98. Pentagastrin-stimulated gastric acid and the recurrence rate in a prospective study of duodenal ulcer patients treated by vagotomy

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In a prospective study of 906 duodenal ulcer patients allocated randomly to either parietal cell vagotomy or selective gastric vagotomy (The Århus County Vagotomy Trial) the pentagastrin-stimulated acid secretion capacity was investigated before, at 3 months and at 1 year after the operation. The clinical status was assessed once a year. This study aims to investigate a possible relationship between the preoperative acid secretion and the alteration in acid secretion during the first year following vagotomy and to compare the secretion pattern to the recurrence rate.

The data from 754 patients are analysed. They were divided into three groups according to the reduction in the pentagastrin-stimulated peak acid output (PAO_{pg}) as measured 3 months after the operation. In 77 patients (10 per cent) the reduction was less than 20 per cent and in 303 patients the reduction was 20–60 per cent, while the reduction was greater than 60 per cent in 374 patients (50 per cent). Patients with the greatest postoperative reduction had the highest preoperative PAO compared to those with poor or no reduction ($P<0{\cdot}0004$). This pattern was identical after PGV and SGV. A highly significant rise in PAO from the third to twelth month was found in the group with the initial reduction of more than 60 per cent ($P<0{\cdot}0001$). In the group with no reduction a decrease of 23 per cent was seen in the mean PAO during the first year of observation ($P<0{\cdot}0001$). No alteration occurred in the mean values for the patients in the intermediate group.

The variation in basal acid secretion showed the same pattern.

The patients in the three groups showed identical dispersion on the Visick scale. The recurrence rate up to date is 7·3 per cent in the series, but 14 per cent in the group with no reduction against 4 per cent in the group with more than 60 per cent reduction ($P<0{\cdot}0005$). The recurrence rate in the intermediate group was 9·6 per cent.

The degree of postoperative reduction in gastric acid secretion and its variation with time seems to reflect biological differences more than difference in surgical technique. The highest recurrence rate was found in the group with no reduction.

99. Effect of histamine and histamine antagonists on acid secretion and mucosal blood flow in man

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Gastric mucosal blood flow (GMBF) and acid secretion increase together during stimulation with pentagastrin (Knight et al., 1978). The purpose of this study was to investigate the effect of histamine on acid and GMBF in man, with and without H_1 and H_2 receptor blockade.

Seven male volunteers (aged 22–36) were given histamine in four doses ($1{\cdot}57$–$12{\cdot}2\times10^{-6}$ mol kg^{-1} h^{-1}) each for 30–45 min. The studies were repeated with an infusion of either mepyramine ($2{\cdot}5\times10^{-6}$ mol kg^{-1} h^{-1}) beginning 30 min before histamine. Maximal output of acid and of GMBF (estimated using neutral red clearance) was calculated, as well as the dose of histamine giving half-maximal output (ED_{50}) according to Parker and Waud (1971). Maximal acid output was $310\pm21{\cdot}1$ µmol H^{+} min^{-1} and GMBF was $58\pm3{\cdot}9$ ml min^{-1}.

The ED_{50} (mean±s.e. mean) is given in the Table.

$ED_{50}\times10^{-6}$ mol kg^{-1} h^{-1}	Acid	GMBF
Histamine	$3{\cdot}4\pm0{\cdot}66$	$2{\cdot}4\pm0{\cdot}39$
$^{+}$mepyramine	$2{\cdot}8\pm0{\cdot}57$	$1{\cdot}4\pm0{\cdot}21$
$^{+}$cimetidine	$9{\cdot}3^{**}\pm0{\cdot}88$	$2{\cdot}8\pm0{\cdot}41$

** $P<0{\cdot}05$ compared to histamine alone (analysis of variance compared to regression).

Mepyramine had no effect on either acid or GMBF and at the dose used cimetidine did not affect GMBF. We conclude that the gastric vasculature is less sensitive to cimetidine than the parietal cell in man.

KNIGHT S. E., MCISAAC R. L. and FIELDING L. P. (1978) The effect of highly selective vagotomy on the relationship between gastric mucosal blood flow and acid secretion in man. *Br. J. Surg.* **65**, 721–723.

PARKER R. B. and WAUD D. R. (1971) Pharmacological estimation of drug receptor dissociation constants: statistical evaluation. *J. Pharmacol. Exp. Ther.* **177**, 1–12.

100. Total body hyperthermia induced by a computerized microwave technique: studies in normal and tumour-bearing rats

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The selective lethal effect of supranormal temperature on malignant cells is well documented. Different methods of hyperthermia to induce tumour necrosis have been developed —water bath immersion, microwave, ultrasound and hyperthermic regional perfusion. Most information on microwaves concerns application for local hyperthermia. The temperature and length of exposure and how to fractionate the microwave heat for maximum tolerance and effectiveness are not established. In this communication total body hyperthermia induced by microwave has been tested.

Wistar rats (200 g), with or without transplantable adenocarcinoma in the liver, were used under ether anaesthesia. A Pt/Ir thermocouple was placed retroperitoneally adjacent to the aorta with the tip below the diaphragm. The animals were kept isolated in a plexiglas cage, which was placed in a larger plexi cage with a constant temperature (25 °C). Siemens (Radioterm 305) Magnetron at 2·45 GHZ max and 200 W microwave generator was used. The exposure was below 4000 W/m^2. The temperature probe signal from the animal was digitalized and fed to a computerized control system (INTEL 8085 microprocessor) with 16 Kbyte memory. This system directed the microwave generator through a set of relays to a predetermined temperature in the animals of 41·5 °C or 42 °C for 1 or 2 h three times per 24 h. The microwave generator was turned off for a period of 4 s before the temperature reading to avoid microwave-induced interference. The temperature was recorded each 30 s. The temperature in the animals was also recorded in other parts of the body. The influence of hyperthermia on the survival and on tumour growth was registered.

The computerized microwave generator induced a precise hyperthermia (±0·2 °C) to a predetermined temperature for exact duration and intervals. The temperature registered in other parts of the body varied in relation to the guiding probe (±1 °C). The central temperature of 41·5 °C for 1 h three times per 24 h caused a 70 per cent survival. Longer duration or higher temperature increased the mortality significantly. No difference in survival between tumour-bearing and non-tumour-bearing rats was seen. A reduced tumour growth was observed during the first 3 days after hyperthermia.

A computerized microwave technique has been shown to induce a precise hyperthermia in experimental animals. The central temperature of 41·5 °C for 1 h three times per 24 h gives acceptable mortality in the experimental animals. A reduced tumour growth after this type of hyperthermia was observed.

101. Thyrotropin (TSH) binding and adenylate cyclase stimulation in normal and adenomatous thyroid tissue

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Previous studies showed that TSH binds to TSH receptors both in normal and neoplastic thyroid tissue. This investigation compared TSH binding with a known biological action of TSH; i.e. adenylate cyclase (AC) responsiveness to TSH ^{125}I bovine TSH (specific activity 11 to 15 μCi/μg) was incubated with an 8000 *g* particulate fraction of normal (NT) or adenomatous (A) thyroid tissue rich in thyroid plasma membranes. AC stimulation, and protein concentration, were measured by standard methods.

Results: 1. Total TSH binding amounted to 9·26 per cent of total radioactivity for NT and 13–19 per cent for A. Non-specific binding was 0·5–1·3 per cent. 2. Total binding reached a plateau within 30 min at 30 °C and remained stable in both NT and A for 3 h. 3. Particulate fractions prepared from frozen tissue showed a marked decrease in TSH-stimulated AC but TSH binding persisted. 4. AC stimulation (per mg prot.) in response to TSH and fluoride was about three times greater in frozen 8000 *g* particulate prepared from fresh thyroid tissue when compared to whole homogenate. 5. Basal AC activities (pmol/30 mg prot.) in NT 15·0±1·0 and A 11·3±8·1 (mean±s.d.) were comparable. 6. The TSH concentration required to produce half maximal TSH stimulation of AC was comparable in NT and A (3·5 mU/ml) but maximal stimulation in A was always equal or greater than in NT. 7. Hormone specificity of the TSH receptor was demonstrated since TSH binding was not inhibited and AC not stimulated by hGH, hFSH or hLH. 8. NT and A generally had two orders of binding sites. 9. Binding dissociation constants for high and low affinity sites in NT (Kd_1 $4·8\times10^{-10}$, Kd_2 $4·5\times10^{-8}$) and A (Kd_1 $3·1\times10^{-10}$), (Kd_2 $6·8\times10^{-8}$) were comparable but binding capacities (pg/μg particulate protein) were higher in NT (n_1 57·6, n_2 3750) than in A (n_1 14·9, n_2 708).

It is concluded that (*a*) benign thyroid adenomas have TSH receptor sites that exhibit a biological response (AC stimulation) to TSH; (*b*) Adenomas have fewer high affinity binding sites but greater AC stimulation to TSH than NT; (*c*) TSH binding and AC stimulation can occur under the same experimental conditions.

102. The patient with abdominal pain and negative investigations: discharge or laparoscopy

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The patient discharged from hospital with undiagnosed abdominal pain has a 56·9 per cent chance of more pain within 3 years and in the over 50s age-group a 10 per cent chance of subsequently developing cancer (McAdam et al., 1978). A series of patients is reviewed with chronic persistent or recurrent abdominal pain and a negative barium meal and follow-up examination referred by consultant physicians for a surgical opinion.

There were 102 patients, age range from 17 to 70 years (mean age 46). All patients were laparoscoped under general anaesthetic with CO_2 insufflation. The findings in the peritoneal cavity were noted and if laparotomy was thought necessary, this was performed under the same GA. Follow-up of the rest of the patients was from 4 years to 6 months. Significant pathology other than adhesions and ovarian cysts was observed in 25 patients. These included inflammatory bowel disease, 5 patients (mean age 33) and intra-abdominal malignancy, 7 patients (mean age 64). The diagnosis was missed in 2 patients despite laparoscopy.

The results of this survey indicate that 25 per cent of patients with chronic persistent abdominal pain are found to have significant intra-abdominal pathology and that laparoscopy is a reliable investigation in establishing a firm diagnosis in these patients.

MCADAM W. A. F., WILSON D. H., MATHARU S. A. et al. (1978) Once a bellyacher, always a bellyacher? *Br. J. Surg.* 65, 818.

103. Delayed hypersensitivity response (DHR) and infections in surgical cancer patients

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Failure of DHR has been shown to be associated with an increased incidence of sepsis in surgical patients. The purpose of this study has been to evaluate DHR and the incidence of postoperative infections in surgical cancer patients. One hundred and fifty patients, 20–78 years old, with the preoperative diagnosis of cancer (stomach, 37; colon and rectum, 37; oesophagus, 4; pancreas, 7; breast, 24; lung, 18; melanoma, 12; skin, 6; hepatoma, 1; ovary, 1; uterus, 2; sarcoma, 1) have been skin tested before surgery with recall antigens (RA) and a primary antigen (PA). RA: intradermal injection of PPD, trichophyton, candida and streptokinase–streptodornase. PA: epicutaneous sensitization and challenge with DNCB. Readings were recorded by the same observer as mm of erythema and induration, and the responses were graded as: normergic, hypoergic and anergic. In order to identify possible causes of anergy and infection, the following parameters have been considered: preoperative serum albumin level, tumour stage, duration of anaesthesia and operative contamination. Fifty-four patients were recorded as normergic, 63 hypoergic and 12 anergic. The following surgical infections have been observed: urinary (26), respiratory (23), wound (20), thrombophlebitis (6), intra-abdominal abscess (6), central venous catheter (6), biliary (1), postoperative undiagnosed fever (10). One or more of these infections occurred in 37 per cent of the normergic patients, in 46 per cent of the hypoergic patients and in 83 per cent of the anergic patients. The incidence of infections in anergic patients is significantly higher than in the normergic group ($\chi^2 = 6·7$; $P<0·01$) and hypoergic ($\chi^2 = 4·2$; $P<0·05$) groups. Albumin concentration was significantly lower in anergic patients than in normergic (3·14±0·45 g/100 ml *v.* 3·50±0·46 g/100 ml; $P<0·05$). No correlation was found between DHR and stage of tumour. The incidence of respiratory infections only is significantly higher when duration of anaesthesia is longer than 120 min ($P<0·05$). In normergic patients the degree of operative contamination is associated with a significantly higher incidence of infections (infections in clean operation *v.* contamined: $\chi^2 = 5·2$; $P<0·05$); however, in anergic patients the incidence of infections is not different between clean and contamined procedures. In conclusion, cancer patients who are preoperatively anergic to skin tests present a higher risk of postoperative infections, regardless of degree of contamination. Anergy seems to be related more to nutritional status than to tumour stage.

104. Trial of adjuvant immunotherapy with *Corynebacterium parvum* in colorectal cancer

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Corynebacterium parvum is a potent stimulator of the reticulo-endothelial system, and is able to boost anti-tumour immunity in animal models. Patients with colorectal cancer have a poor prognosis even after curative surgery (Gill and Morris, 1978). Furthermore, many patients with colorectal cancer show a relative anergy even at early stages of the disease. Thus there is a rational basis for a controlled trial of immunotherapy in colorectal cancer aimed at treating microscopic disease presumed present at the time of surgery.

Patients with Dukes' B or C colorectal cancer were entered into the trial. Those over the age of 70, or known cases of cardiorespiratory disease or a history of allergies, were excluded from the trial. Patients were randomized into treatment with *C. parvum* or no treatment. Informed consent was obtained from patients receiving *C. parvum*. They were given killed *C. parvum* (Wellcome) i.v. at doses of $5\ \mathrm{mg/m^2}$ in normal saline over 30 min. Ten infusions were given over 2 years. Most patients suffer shivering accompanied by pyrexia 2–3 h after infusion and some become hypotensive in the first 12 h. A transient leucopenia and a depression in T lymphocyte numbers and PHA responsiveness occurred after the infusion, returning to normal levels within 48 h. However, a significant increase in blood monocytes, the precursors of macrophages, was seen at 7 days. To date 72 patients have been entered into the trial with the following outcome.

	Patients	Recurrences	Tumour deaths
C. parvum	34	5	2
No treatment	38	8	5

The trial is continuing, but it does not appear that *C. parvum* infusions are deleterious to patient outcome, and there is a suggestion of a beneficial influence.

GILL P. G. and MORRIS P. J. (1978) The survival of patients with colorectal cancer treated in a regional hospital. *Br. J. Surg.* **65**, 17–20.

105. The effect of diversion of duodenal contents on the production of experimental gastric ulcer

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The production of chemically induced gastric cancers in rats is enhanced following vagotomy and gastroenterostomy (Morgenstern, 1968). This and similar operations in man are allegedly followed by a significant increase in the development of gastric cancers (Gazzola and Saegesser, 1975). Reflux of biliary and pancreatic secretions is said to be a contributing factor in the induction of these neoplasms. The present study was designed to test whether diversion of duodenal contents after vagotomy and gastroenterostomy would decrease the expected incidence of experimental gastric carcinomas in rats.

Two hundred and forty animals were divided into three groups of 80 each: group 1 animals (controls) had 0·9 mg of 3-methylcholanthrene injected submucosally into the gastric antrum. Group 2 animals (TV+GE) underwent bilateral truncal vagotomy and gastroenterostomy; the carcinogen was injected into the gastric submucosa near the anastomosis. Group 3 animals (TV+GE+Div) were prepared precisely as group 2 animals except that total duodeno-enteric diversion was added. After 8 months, all surviving animals were sacrificed and studied. Blind histopathological examination of the injection site disclosed:

Group	Surviving operations	Death after 1st week*	Developed cancer
1. (Control)	60	0	6 (10%)
2. (TV+GE)	71	4	23 (33%)
3. (TV+GE+Div)	27	4	7 (26%)

* χ^2 not significant at 0·1.

Groups 2 and 3 had an increased incidence of gastric cancer compared to group 1 ($P = 0{\cdot}012$). Groups 2 and 3 did not differ from one another in this regard ($P = 0\ 8$).

The data confirm a greater incidence of chemically induced gastric adenocarcinoma in rats that underwent vagotomy and gastroenterostomy. However, diversion of duodenal contents away from the gastroenterostomy does not protect the animal from this increased risk.

GAZZOLA L. M. and SAEGESSER F. (1975) Cancer of the gastric stump following operations for benign gastric or duodenal ulcers. *J. Surg. Oncol.* **7**, 293–298.
MORGENSTERN L. (1968) Vagotomy, gastroenterostomy and experimental gastric cancer. *Arch. Surg.* **96**, 920–923.

106. Effect of prostaglandin inhibitors and diphosphonates on tumour-mediated osteolysis

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Previous studies have indicated that there are two phases to the bone destruction which occurs with skeletal metastases. The earlier phase is mediated via the osteoclast, the tumour-secreting osteoclast stimulating factors, which include prostaglandin. In animal experiments prostaglandin inhibition has significantly reduced the prostaglandin activity in the tumour, osteoclast production and the amount of bone destruction.

The current studies were designed to determine whether prostaglandin inhibitors had an effect on human tumours and whether other agents which affect osteoclast production but do not affect prostaglandin activity inhibit tumour osteolysis. One mm cubes taken from 27 mammary cancers were cultured against mouse calvarium, different prostaglandin inhibitors, in varying dosage, being added to the culture medium (Table). In 15 experiments diphosphonates were added. These drugs directly affect bone turnover.

Twenty specimens of the VX2 carcinoma were studied in the same way. The results (Table) indicated that prostaglandin inhibitors produced a significant reduction in tumour osteolysis. Diphosphonates were as effective but combining the two agents did not enhance the effect.

The findings suggest that agents which inhibit osteoclast production will reduce tumour-mediated osteolysis irrespective of their mechanism of action.

	Mammary cancer	V×2
Control	0·83±0·12*	0·9±0·12
Prostaglandin inhibitors		
Indo. (1×10^{-3} M)	0·40±0·11	0·22±0·07
Indo. (1×10^{-4} M)	0·48±0·12	0·26±0·09
Indo. (1×10^{-5} M)	0·21±0·09	0·25±0·11
Ibupro.	0·42±0·11	0·27±0·09
Flurbipro.	0·46±0·13	0·29±0·07
Diphosphonate		
EHDP	0·23±0·12	0·33±0·11
Cl. 2DMP+	0·22±0·12	0·24±0·07
indo.	0·37±0·11	0·24±0·08

Indo., Indomethacin; Ibupra, ibuprofen; Flurbipro, flurbiprofen.
* Measured as mg Ca release.

107. Kidney graft survival after donor pretreatment in dogs receiving peroperative transfusions

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Kidneys of drug-treated donors have a better survival time compared with controls in several species. In man donor pretreatment gives a better graft survival, according to some authors. The data of several prospective trials on donor pretreatment, however, made the benefit of the treatment questionable. Little is known about the mechanisms which underlie the retarded rejection induced by donor pretreatment.

We investigated the *in vivo* effect of a peroperative transfusion with 100 ml fresh complete donor blood, 100 ml leucocyte-free donor blood (erythrocytes, thrombocytes and plasma) and with pure lymphocytes obtained from 100 ml donor blood on pretreated kidneys in dogs. The kidney graft survival data of these groups were compared with the data of untreated kidneys in recipients receiving 100 ml donor blood peroperatively and of pretreated kidneys in recipients receiving 100 ml third party blood peroperatively.

Pretreatment consisted of 50 mg/kg BW procarbazine and 50 mg/kg BW methylprednisolone 5 and 2½ h before harvesting. Donor blood was taken from the donor just before treatment.

	Mean survival	No.
1. Donor pretreatment	26·7	7
2. Donor pretreatment + 100 ml donor blood	12·1	6
3. Donor pretreatment + 100 ml leucocyte-free blood	12·7	7
4. Donor pretreatment + pure lymphocytes of 100 ml blood	13·1	7
5. Donor pretreatment + 100 ml third party blood	18·8	6
6. Control + 100 ml donor blood	12·0	7
7. Control	13·0	8

All recipients received postoperatively 2 mg/kg BW azathioprine, 2 mg/kg BW prednisolone every day.

Our results showed that a peroperative transfusion with a relatively large dose of donor specific antigens with or without active lymphocytes or a relatively small dose of donor specific lymphocytes abolished the improved graft survival induced by donor pretreatment.

In contrast with these results the survival time of pretreated kidneys with a peroperative transfusion with a relatively large dose of third party specific antigens and active lymphocytes was significantly prolonged and did not differ significantly from the survival time of donor pretreatment alone.

108. The role of thymus and spleen in enhanced allograft survival

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The role of the thymus and spleen in enhanced allograft survival is unclear (Tilney and Bell, 1974; Stuart et al., 1976; Batchelor et al., 1977; Tilney et al., 1978). Lewis rats reject L×BN hearts in 7 days. Graft survival is enhanced to 22 days by pretreatment with BN splenocytes and Lewis anti-BN antisera 11 and 10 days before transplantation, respectively. Splenectomy prior to enhancement decreased graft survival to 15 days ($P<0.05$). When splenectomy was delayed until (*a*) just after enhancement, (*b*) at the time of grafting or (*c*) 1 week after grafting, graft survival was unaffected. However, splenectomy 14 days after grafting prolonged graft survival (MST >40 d, 40 per cent surviving >80 d). Thymectomy before enhancement or at the time of grafting did not affect graft survival. Thymectomy 6 or 10 d after grafting decreased enhanced graft survival. Thymocytes harvested from these rats 6 days after transplantation transferred prolonged graft survival to unmodified rats (MST = 17 d). Thus, the spleen is required for optimal initiation of enhancement via antigen and antibody pretreatment. Following grafting the thymus is involved in maintaining enhanced graft survival and the spleen in terminating it.

BATCHELOR J. R., BRENT L. and KILSHAW P. S. (1977) Absence of suppressor cell from rats bearing passively enhanced kidney allografts. *Nature* **270**, 522–524.

STUART F. P., MCKEARN T. J. and FITCH F. W. (1976) Immunological enhancement of renal allografts by anti-receptor antibody. *Surgery* **80**, 130–136.

TILNEY N. L. and BELL P. R. F. (1974) Studies on enhancement of cardiac and renal allografts in the rat. *Transplantation* **18**, 31–37.

TILNEY N. L., GRAVES M. J. and STROM T. B. (1978) Prolongation of organ allograft survival by syngeneic lymphoid cells. *J. Immunol.* **121**, 1480–1482.

109. Potential relationship between Ir genes and Ia antigens expressed on antigen-presenting macrophages

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The immune response to thymus-dependent antigens depends on the presence of Ir genes located within the I region of the H_2 major histocompatibility complex. The I region also controls expression of membrane alloantigens (Ia) expressed on lymphocytes and antigen-presenting macrophages (Mϕ). Experiments were conducted to examine the relationship of Ir genes to Ia antigens at the level of Mϕ-T cell interaction during induction of an antibody response.

Antigen-presenting Mϕ were purified from spleens of [B10.A(3R)×B10.A(5R)] F_1 mice, two strains that differ only at the I–J subregion or in other experiments from [B10.S(9R)×B10.HTT] F_1 mice which also differ at I–J. T–B cells were purified from each parental strain and from F_1 spleens. Mϕ (J^k/J^b) or $\overline{J^k/J^s}$) were incubated with B10.A(3R) anti-B10.A(5R) sera (anti-J^k) for 30 min, washed with fresh media and cultured with the different T–B cell sources plus burro red cells. The number of plaque-forming cells (PFC) was determined on day 5.

F_1 Mϕ blocked with antibodies to I–J	T–B cell source	[PFC/dish ± s.d.] Exp. 1	Exp. 2
Inappropriate anti-Ia	F_1	799±48	670±46
Inappropriate anti-Ia	B10.A(5R)	699±9	649±10
Inappropriate anti-Ia	B10.A(3R)	618±68	697±72
Anti-I–J^k	F_1	776±43	624±25
Anti-I–J^k	B10.A(5R)	56±18	4±3
Anti-I–J^k	B10.A(3R)	901±46	654±14

	T–B cell source	[PFC/dish ± s.d.] Exp. 1	Exp. 2	Exp. 3
Inappropriate anti-Ia	F_1	1209±57	1832±163	808±72
Inappropriate anti Ia	B10.S(9R)	1020±98	1591±42	898±40
Inappropriate anti-Ia	B10.HTT	1193±5	1528±46	890±27
Anti-I–J^k	F_1	1139±40	1601±50	797±56
Anti-I–J^k	B10.S/9R)	499±82	711±71	212±11
Anti-I–J^k	B10.HTT	1074±77	842±117	655±52
Anti-I–J^s	F_1	1139±65	1548±100	696±33
Anti-I–J^s	B10.S(9R)	1251±106	1456±71	801±89
Anti-I–J^s	B10.HTT	489±20	488±54	42±28

F_1 appropriate for experiment: [B10.A(3R)×B10.A(5R)] F_1 or [B10.S(9R)×B10.HTT] F_1.
All results: mean quadruplicate cultures ± s.d.

These results support the concept that the T cell possesses a restricted receptor which must recognize an appropriate I–J subregion determinant on the Mϕ for efficient induction of a primary antibody response and suggest a mechanism of Ir gene function.

110. Effect of ALG on suppressor-lymphocytes *in vitro* (cultures) and *in vivo* (kidney transplant patients)

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The suppressive activity of regulator-lymphocytes is supposed to play a beneficial role in protecting a graft from rejection. As immunosuppressive therapy (IST) in kidney transplantation reduces lymphocytes (LY) in peripheral blood (PB), especially when combined with ALG, it was the aim of this study to monitor the fluctuations of LY populations in respect to suppressor cell function under such a therapy.

Thirty-five kidney recipients received a combination of 5 mg/kg BW azathioprine 100 mg prednisolone reduced to 30 mg after 2 months and ALG, 20 mg protein/kg BW over 10 days after transplantation. A basic therapy of 2·5 mg azathioprine and 15 mg cortisone was continued for 8 months. WBC-count shifting of T–B cells in PB, circulating levels of ALG and ALG bound to LY surface were monitored at 3-day intervals. The effect of IST and the action of ALG only, on 'Suppressor cells', was measured in an *in vitro* assay with patients' peripheral LY and cells from healthy donors. This suppressive influence of 'spontaneous' and 'Concavalin A activated' circulating suppressor cells on patients on MLC and mitogen stimulation (PHA, PWM, Con A) was recorded preoperatively, under IST with and without ALG, and during rejection episodes. The effect of various concentrations of ALG-LY of healthy donors was measured with 'MLC-specific' suppressor cells' in MLC and mitogen stimulation.

			R	
		Preop.	No ALG	ALG
MLC/Spont.	Lys*	24%	+134%	+130%
MLC/Activ.	Lys	41%	13%	19%
PHA/Spont.	Lys	29%	14%	+132%
PHA/Activ.	Lys	39%	50%	27%

			No R	
			ALG	No ALG
MLC/Spont.	Lys*	24%	+117%	31%
MLC/Activ.	Lys	41%	4%	59%
PHA/Spont.	Lys	29%	21%	46%
PHA/Activ.	Lys	39%	30%	54%

R, Rejection.
* Lys ≙ Spontaneous and activated suppressor lymphocytes.

No changes in cell counts and activity were found preoperatively. After transplantation and especially after ALG, LY counts drop to 40 per cent of initial values. As B cells remain relatively constant, T cells show the major reduction. ALG positive circulating LY decrease from 70 per cent preoperatively to 30 per cent after 7 days of ALG therapy. This reduction seems to include not only cytotoxic effect LY but also suppressor cells. Preoperatively values of spontaneous and activated suppressor cells are reduced during rejection, also in patients with rejection crises treated with ALG. In most patients the suppression of MLC and PHA response shifts to stimulation. Patients with well functioning grafts only under basic therapy recover quickly to show normal suppression. As ALG reduces the suppressive activity *in vivo*, tests were performed with ALG *in vitro*. LY incubated with LAG+rabbit complement for 1 h lose their MLC 'specific' and 'unspecific' suppressive activity with increasing ALG concentration. The results indicate, that IST and ALG hits cytotoxic as well as suppressor cells in patients and they show that the suppressive activity recovers quickly after reduction of IST or ALG.

111. Immune complex disease in mice and humans given *Corynebacterium parvum*

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Repeated infusions of *C. parvum* are used to treat human cancer. Renal failure has been reported in 3 patients (Dosik et al., 1977). In parallel studies in mice and humans we determined the effects of repeated doses of *C. parvum* on production of immune complexes and associated disease.

Mice received intravenous injections of 70 μg (human-equivalent dose) at weekly intervals for 4 weeks. Control groups were given a single low dose (70 μg) or a single high dose (466 μg) or no treatment. Thirty cancer patients were studied: 15 received *C. parvum* (10 mg/m²) by intravenous infusion monthly for 4 months; 15 received no treatment (controls).

Mice: Circulating immune complexes determined by Clq binding assay were significantly increased in mice that received repeated doses.

Immunofluorescent staining showed C(3) and IgG deposition in the kidneys and histology revealed a marked proliferative glomerulonephritis. These mice had microscopic haematuria but no elevation of serum urea.

Humans: Clq immune complexes were detected in those treated with *C. parvum*; 3 developed mild proteinuria and 12 microscopic haematuria with red cell and hyaline casts, the changes resolving over 3 days. Serum urea and creatinine remained normal.

We conclude that in mice repeated doses of *C. parvum* cause circulating immune complexes which are deposited in the kidneys causing renal disease. A similar pathology seems likely in humans.

DOSIK G., GUTTERMAN J., HERSH E. et al. (1977) Immunotherapy with intravenous *C. parvum*, nephrotoxicity. AACR Abstracts, 75.

112. Human K cell cytotoxicity is largely mediated by a T cell subset

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Both the surface receptors and the mechanisms of cytolysis of T (E-rosette and LMC cytotoxicity) and K (Fc receptor and anti-body-dependent-cellular cytotoxicity-ADCC) lymphocytes are distinctly different by classic teaching. We observed that anti-thymocyte globulin rendered T cell specific by B cell absorption depressed K cell type cytotoxity (ADCC). We, therefore, performed detailed *in vitro* and *in vivo* studies of the relationship of human T and K cells in macrophage-free cell preparations.

Results: 1. Surface receptor studies—using a sensitized ox erythrocyte rosetting test for Fc receptors, 87±4 per cent of thymocytes and 22±3 per cent of peripheral blood T cells can be shown to have IgM Fc receptors, whereas 33±8 per cent of thymocytes and 21±7 per cent of peripheral blood cells have IgG Fc receptors. 2. Clinical anti-human ATG given to humans causes a marked fall ($P<0{\cdot}05$) in ADCC activity. 3. Clinical ATG rendered T cell specific by B cell adsorptions and shown by *in vitro* testing to have T cell specificity significantly depresses K cell cytotoxicity ($P<0{\cdot}01$). 4. Depletion of human T cells by E rosette sedimentation significantly decreases K cell activity ($P<0{\cdot}05$). 5. Furthermore, the resulting T cell enriched reaction recovered by lysis of sheep cells can be shown to have a significant ($P<0{\cdot}01$) increase in K cell activity over unfractionated peripheral blood cells.

These studies support the concept that, in the human, the Fc receptor cell known to execute the majority of ADCC activity is a subpopulation of T cells. The findings are of theoretical interest and also may be important in developing suppressive agents to block human ADCC activity since surface receptors and function (Fc and ADCC) classically ascribed to K cells in the human are related to a T cell subset activity which appears to be blocked by agents such as ATG which have a relatively high degree of anti-T cell specificity.

113. Modulation of the immune response and control of tumour spread by a new synthetic compound

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114. Collagen formation by arterial smooth muscle cells after injury: an electron microscopic study

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We have shown that collagen accumulates in thickened intima covered by regrowing endothelium following arterial injury (Chidi et al., 1979). We now compare sequential fine structural changes in non-endothelized and endothelized zones to test the hypothesis that endothelial cells (EC) might be a source of collagen. Changes in EC and smooth muscle cells (SMC) were characterized 2–60 days after a standard balloon injury of rabbit thoracic aorta.

In intima under regrowing endothelium, sequential fine structural changes showed transitional forms of SMC acquiring morphologic characteristics of fibroblasts (FB). Ultrastructural alterations of SMC were the development of nuclear lobulation, prominent Golgi and rough endoplasmic reticulum, loss of myofibrillae and appearance of many pinocytic vacuoles near cell membranes. Such changes were accompanied by abundant collagen deposition in close juxtaposition to transformed SMC. In contrast, zones not covered by endothelium exhibited only polygonal less active SMC: here collagen deposition was scanty. The presence of platelets, often within the arterial wall, also supported their postulated role as mediators of SMC proliferation (Ross et al., 1974). No ultrastructural evidence of collagen formation by EC was found.

Regrowing endothelium appears to stimulate transformation of SMC to FB after arterial injury. Collagen fibres selectively accumulate in such areas. Only transformed SMC, and not ECs, appear to secrete collagen after arterial injury.

CHIDI C. C., KLEIN L. and DEPALMA R. G. (1979) Effect of endothelial regeneration on collagen accumulation in the artery after injury. *Surg. Gynecol. Obstet.* (In the press.)

ROSS R., GLOMSET J. A., KARIJA B. et al. (1974) A platelet dependent serum factor that stimulated the proliferation of arterial smooth muscle cell *in vitro*. *Proc. Natl Acad. Sci.* 71, 1207–1210.

115. Wound healing in stomach and duodenum during normal conditions and during long term cortisol treatment

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Few experimental studies have been published on the functional properties of wound healing in stomach and duodenum, confined to measurement of bursting and/or breaking strength. To obtain fuller and more detailed information, complete load-deformation curves were recorded and the development of the distribution of collagen in the healing area was measured. Furthermore, the effect of long term corticosteroid treatment was investigated, as little is known about the effect of these hormones on wound healing in the gastrointestinal tract.

One hundred and fifty male Wistar rats about 5 months old were used. Incisional wounds were made in the stomach (in the non-glandular part or rumen [R], and in the glandular part or corpus [C]) and duodenum [D]. The wounds were immediately resutured with 6/0 propylene interrupted sutures. After 5, 7, 10, 20 and 40 days the sutures were removed and strips perpendicular to the incision line were tested in a materials testing machine. In a second series, strips parallel to the incision line were punched out and collagen distribution was determined. A third series of rats was treated daily with cortisol (8 mg/kg) or NaCl subcutaneously, starting 4 weeks before operation and continued throughout the experiment. Strips from R, C and D were tested 7 and 20 days postoperatively.

Of intact tissues R had the highest breaking energy (area under load deformation curves) as well as highest extensibility and collagen concentration. There were only small differences between C and D except for breaking energy, which in C was twice the value of D. Of healing wounds from C and D both breaking strength and breaking energy were significantly higher than of intact tissues after 40 days. In R breaking strength reached the intact value, while the breaking energy reached only 75 per cent after 40 days. The stiffness of all types of wounds was higher after 40 days compared to intact tissue. The collagen concentration showed a good correlation to the mechanical properties of the wounds and the biochemically active zones were 4–6 mm on each side of the incisional line. Cortisol caused significant decrease in all tissues, the breaking energy (in per cent of the intact tissue value) for R: 16 (7 d) and 29 (20 d) (control wounds: 41 and 62), and for D: 21 (7 d) and 61 (20 d) (control wounds 52 and 106). Cortisol increased the incidence of microabscesses, but no wound ruptures occurred (non-absorbable sutures were used).

The normal healing of wounds in the glandular part of the stomach and duodenum is rapid, and the collagen concentration in these wounds is enhanced. The healing pattern of the non-glandular part of the stomach is different—the increase of mechanical strength is lower as is that of collagen concentration. The wound healing in all types of tissue is significantly impaired by systemic corticosteroid treatment.

116. Intrinsic contractility of human lymphatics is the main factor propelling lymph

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According to the present state of knowledge, interstitial fluid and lymph are transported in man via the lymphatics by extrinsic forces such as muscle contractions, respiratory movements and *vis a tergo*.

We have found that rhythmic intrinsic contractility of subcutaneous lymphatics in the human leg generates pressure waves necessary to propel lymph. Studies were carried out in 12 randomly selected male volunteers. Leg subcutaneous lymph collecting vessels were cannulated against the direction of lymph flow and on day 2–5 after cannulation intravascular end pressures and the lymph flow rate were measured. Pressures were recorded in the upright and horizontal positions, while legs were kept motionless. Low pressure transducer AE 840 (Solid State Products) and Beckman R-611 Dynograph recorder were used. In all investigated subjects rhythmic pulse waves were noted with a frequency of 1–9 s, average 4 s, separated by periods of steady pressure lasting from 15–50 s. However, in some subjects, mostly after prolonged walking, continuous pulsation was observed. The time of each pulse wave was 6–8 s, but in most instances 6 s. The pulse pressures ranged from 1 to 40 mmHg. The highest pulse pressures were noted at low mean pressures (below 50 mmHg). At higher pressures the amplitude of pulse waves seemed to be dampened. Also at high pressures, the frequency of pulsation was higher than at low pressures, and often without relaxation periods. The highest observed intralymphatic end pressure was around 50 mmHg in 9 subjects, 90 mmHg in one and 120 mmHg in two. In 3 men the same rhythm of lymphatic pulse waves as that of the expression of drops of lymph from the end of the cannula was observed. In all cases pulse waves were completely asynchronous with arterial pulse rate, respiratory movements and movements of leg muscles.

The presented observations do not permit any analysis of the nature of the lymphatic pulse. They showed, however, that in human legs lymph can be driven by intrinsic contractions of the lymphatics. These findings may have bearing on the understanding of the transport of protein containing tissue fluid and lymph back to the blood circulation, as well as of oedema formation and of different pathologies of lymph vessels in man.

117. Inhibition of secretion produced by lesser curve myotomy in the dog

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Branches of the nerve of Latarjet run with the serosa of the stomach before penetrating the muscularis (Mitchell, 1940). Myotomy of the pylorus and oesophagus are safe and well-established procedures. Myotomy of the lesser curve of the stomach with preservation of the major vessels should denervate the parietal cell mass. Four dogs with gastric cannulas had pentagastrin infusions (0·375–6 μg kg^{-1} h^{-1} i.v.) each on three separate occasions before and after lesser curve myotomy.

After myotomy in response to pentagastrin there was a shift to the right of acid secretion with a 33 per cent reduction in the peak, a finding similar to that reported after truncal vagotomy (Emas and Grossman, 1967). Total pepsin (Hunt, 1948) secretion was more markedly depressed by myotomy (77·7 per cent) than by truncal vagotomy. Myotomy abolished the secretory response to insulin in three dogs and in one there was a late positive response of small magnitude. Pepsin secretion did not rise above basal levels in response to insulin postoperatively.

Secretory inhibition after lesser curve myotomy is equal to that produced by vagotomy. This would appear to give the operation a sound anatomical and physiological basis, for technically it is easy to perform and obviates the risk of damage to the nerve of Latarjet or of ischaemic necrosis of the lesser curvature.

EMAS S. and GROSSMAN M. I. (1967) Effect of truncal vagotomy on acid and pepsin responses to histamine and gastrin in dogs. *Am. J. Physiol.* **212**, 1007–1012.

HUNT J. N. (1948) A method of estimating pepsin activity in gastrin contents. *Biochem. J.* **42**, 104–109.

MITCHELL G. A. G. (1940) A macroscopic study of the nerve supply of the stomach. *J. Anat.* **75**, 50–63.

118. Technical and functional results after restorative resection of radiation damaged rectum

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Technical and functional results of resectional surgery for the rectal complications of radiation therapy are reported. Thirty-two consecutive patients underwent subtotal rectal resection with restoration of continuity by transanal colo-anal sleeve anastomosis. They comprised 26 patients with rectovaginal fistulas, 3 suffering severe haemorrhage, 2 with rectal strictures and 1 with radiation proctitis and carcinoma. Technical success was obtained in 30 of 32 patients. The amount of rectal muscle wall retained remained fairly constant; the length of mucosa preserved varied.

The ability to retain a water-soluble contrast enema was present in 83 per cent of 30 patients 3 months after surgery. Subjectively, total continence was present in 53 per cent at 3 months, 64 per cent at 6 months and 79 per cent at 1 year. Anastomosis at dentate line level resulted in total continence in 1 of 6, compared to all of 18 when 1–2 cm of mucosa above the dentate line was preserved, assessed 1 year after operation.

Anorectal manometry using open perfused tubes showed the maximum anal resting pressure (cmH_2O) to be significantly higher ($P<0·02$) where preservation of 1–2 cm of mucosa was possible (mean 40·15), compared to those whose anastomosis was at dentate line level (mean 22·83).

119. A mechanism for prostaglandin cytoprotection

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Does dimethyl prostaglandin of the E_2 series protect canine gastric secretory mucosa from aspirin-induced erosive gastritis through stimulation of a sodium-rich alkaline secretion? The mucosa of partitioned chambered segments of canine stomach ($n=9$) were exposed to 20 ml of isosmotic hydrochloric acid, or 20 μg of 16,16-dmPGE_2 or 20 mM of aspirin in isosmotic acid. Counterpressure (CP) of 40 mmHg was placed on the test (T) side of the partitioned chamber. Solutions recovered at 15 min intervals were analysed for changes in volume (V), sodium (Na) and hydrogen (H^+). Mucosal blood flow (MBF) was estimated by radioactive microspheres. Injury was determined by gross inspection and graded 0–5. The results are represented as the mean ± its standard error.

Two control and 6 test mucosas developed gross erosions. The mucosas exposed to counterpressure had more extensive injury (lesion index, control 0·8±0·3 *v.* test 2·0±0·6, $P<0·01$). Thus, the outflow of alkaline secretion which accompanies topical PGE and aspirin was lessened by counterpressure, and the protection offered by PGE compromised. Blood flow also decreased. These results suggest that prostaglandin cytoprotection from aspirin injury may be related in part to filtration of a sodium-rich alkaline secretion.

	HCl/No CP		PGE/No CP		PGE/CP	
	C	T	C	T	C	T
V (μl/min)	14·2	7·3	70·0	62·8	58·6	*29.0
	±5·4	±1·6	±15·4	±14·3	±5·9	±5·9
Na (μmol/min)	2·7	2·4	15·9	14·5	15·3	*8·9
	±1·1	±0·7	±3·3	±3·1	±2·3	±2·1
H^+ (μmol/min)	−0·6	−1·1	−3·1	−4·9	−3·7	−3·8
	±0·5	±0·9	±0·7	±0·9	±0·8	±1·2
MBF (ml/min)			1·5	1·6	1·5	***0·8
			±0·2	±0·3	±0·2	0·1

	ASA/CP		HCl/CP	
	C	T	C	T
V (μl/min)	117·7	*73·8	98·5	*49·1
	±19·3	±17·7	±18·5	±13·0
Na (μmol/min)	31·3	*21·0	27·0	*16·4
	±5·0	±4 3	±4·6	±2·9
H^+ (μmol/min)	−7·6	−8·1	−8·8	−6·8
	±0·9	±1·4	±1·9	±1·5
MBF (ml/min)	1·4	**0·9	1·7	**1·1
	±0·2	±0·2	±0·3	±0·4

Significance (*t* test) from control (C) $*P<0·05$, $**P<0·01$, $***P<0·001$.

120. The effect of surgical operation upon phagocytosis by monocytes

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Increasing attention is being paid to the role of the mononuclear phagocytic system (MPS) in the immune process, particularly in relation to cancer and organ transplantation. Although the effect of surgical operation upon colloid clearance by the 'fixed' cells of the MPS, and upon the function of lymphocytes and granulocytes, has been studied, the circulating component of the MPS—the monocyte—has received little attention.

In this study, monocytes were isolated from the blood of patients undergoing surgery mainly for benign disease and the uptake by these cells of ^{99}Tc-labelled latex particles assessed using a modification of a previously described technique (Al-Ibrahim et al., 1976). Healthy volunteers served as controls. Lymphocytes and monocytes were separated from the blood, following which the monocytes were counted using a specific stain and allowed to adhere to glass coverslips. Results were expressed as the percentage uptake of a known added amount of ^{99}Tc latex.

The results (Table) show that a marked increase in phagocytosis occurs by 24 h following surgery ($P=0·01$), with a return towards normal values by 48 h. In another group of patients studied at 1 h postoperatively no change in monocyte function was observed, a finding which is in contrast to previous studies on the 'fixed' MPS reporting diminished function at this time.

Table: PERCENTAGE UPTAKE OF ^{99}Tc-LABELLED PARTICLES (mean±s.d.)

	No.	Preop.	1 h postop.	24 h postop.	48 h postop.
Patients	10	0·48		1·35*	0·55
		±0·44		±1·13	±0·49
	8	0·95	0·92		
		±0·27	±0·27		
Controls	10	0·33		0·35	0·24
		±0·25		±0·12	±0·075

* $P=0·01$ of Preop. (Wilcoxin signed rank test).

AL-IBRAHIM M. S., CHANDRA R., KISMORE R. et al. (1976) A micromethod for evaluating the phagocytic activity of human macrophages by ingestion of radio-labelled polystyrene particles. *J. Immunol. Method* **10**, 207–218.

121. Serum-mediated and cell-dependent post-thermal injury hypermetabolism

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Increased basal metabolic rate, protein catabolism and body weight loss characterize the metabolic response to major thermal injury in man and rats. The mediators and the organ system and cellular expression of the hypermetabolism are poorly understood. The post-thermal injury metabolic response of liver and white cells and the role of serum as an effector of these responses is evaluated by *in vitro* tissue slice and cell suspension oxygen consumption determinations following 50 per cent full-thickness scald burns in rats.

The oxygen consumption of 20 burned and 20 sham-burned 540-g rats was determined between days 10 and 15 post burn at ambient temperatures of 31±1·5 °C at 100 per cent humidity during 1½ h study periods in closed metabolic chambers. On the fifteenth day post burn the rats were sacrificed, 15 ml of heparinized blood obtained from each rat and plasma decanted. Purified leucocytes were prepared by treatment with ammonium chloride and differential centrifugation in Ficol-Hypaque to separate leucocytes from lymphocytes and monocytes. Livers were removed and 100-μg tissue slices were prepared with a Stadie Riggs microtome. Oxygen consumption of liver slices and white blood cell suspensions from burned and control rats were determined in aliquots of both burn and control serum with a Yellow Springs electrode oxygen metre at 37·5 °C equilibrated with 100 per cent oxygen. Determinations were corrected to standard temperature and pressure and expressed as $\mu l\ mg^{-1}\ h^{-1}$ for liver slices and $\mu l\ 10^{-6}$ cells h^{-1} for leucocytes. Statistical comparisons were made by four-way analysis of variance.

The burned rats prior to sacrifice were 45 per cent hypermetabolic relative to controls (burns oxygen consumption = 1·25±0·12, controls = 0·86±0·01 $ml\ g^{-1}\ h^{-1}$, $P<0{\cdot}001$). The metabolic rate of burn white blood cells is depressed to 43 per cent that of the controls ($P<0{\cdot}01$). This response was not serum-dependent. Burn and control livers were made 13–25 per cent hypermetabolic by incubation in burn serum ($P<0{\cdot}01$) but were not inherently different.

	Controls	
	C plasma	B plasma
Leucocytes	1·90±0·42	1·95±0·31
Liver slices	2·83±0·095	3·22±0·14

	Burns	
	C plasma	B plasma
Leucocytes	0·834±0·088	0·818±0·094
Liver slices	2·88 ±0·095	3·57 ±0·17

Oxygen consumption values = $\mu l\ 10^{-6}$ cells h^{-1} for leucocytes and $\mu l\ mg^{-1}\ h^{-1}$ for liver slices.

C, Control; B, burn.

In burned rats a plasma factor induces liver hypermetabolism, concomitant white blood cell hypometabolism is cell origin dependent. Definition of the plasma mediator may allow modulation of its hypermetabolic effects.

122. The effects of chronic volume overload on the diastolic mechanics of the left ventricle

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Chronic volume overload (CVO) produces concentric left ventricular hypertrophy and dilatation associated with a shift to the right of the diastolic pressure-volume (PV) curve suggesting increased left ventricular (LV) compliance.

However, it is unclear whether this change in the diastolic filling properties results from altered intrinsic myocardial elastic properties (stress–strain relationship), or if it results simply from changes in ventricular geometry. To investigate this relationship chronic volume overload was produced in 6 adult mongrel dogs by creation of an 8-mm aortocaval shunt. In order to assess precisely dynamic LV geometry, dimension transducers were implanted 3–5 months later to measure minor and major axis diameters and equatorial wall thickness. LV transmural pressure was determined from measurements of left ventricular and pleural pressures. Pressure and dimension data were used to obtain the diastolic PV and stress–strain relationships and data from chronic volume overloaded animals were compared with data from normal (NL) dogs. The cardiac index was increased (8·4±0·9 $l\ min^{-1}\ m^{-2}$ in CVO *v.* 2·8±0·2 $l\ min^{-1}\ m^{-2}$ in NL). Normalized left ventricular mass was 6·2±1·1 g/kg body weight (NL = 3·9±0·2). The static diastolic PV curve in chronic volume overload was shifted to the right when compared with control animals indicating an increased diastolic LV chamber compliance. However, the diastolic myocardial elastic properties characterized by the diastolic stress–strain relationship remained entirely normal. These data indicate that the altered diastolic filling properties observed in compensated chronic volume overload result entirely from changes in ventricular geometry and not from changes in the material properties of the myocardium.

123. Liver tolerance to normothermic ischaemia: an experimental study in the pig

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The liver does not tolerate more than 15 min of normothermic ischaemia. This classic concept based on experimental data has recently been challenged by reports of good tolerance to one hour's normothermic ischaemia in dogs or pigs (portal triad occlusion and splanchnic vein decompression) and humans (portal triad occlusion). The present study intends first to elucidate these apparent discrepancies and secondly to determine the maximum safe period of hepatic normothermic ischaemia.

Twenty-nine pigs, divided in 5 groups, were submitted to complete liver inflow occlusion. Group 1, 8 pigs; portal triad clamping of 45 or 60 min. (In all other groups intestinal veins were decompressed through a splenojugular external bypass during portal triad occlusion.) Group 2, 8 pigs, 60 min; group 3, 5 pigs, 90 min; group 4, 5 pigs, 120 min; group 5, 3 pigs, 180 min. No liver refrigeration was used. Liver specimens were taken before ischaemia, 20 min and 1 month after revascularization.

All animals in groups 1 and 5 died; all animals in groups 2, 3 and 4 survived. Changes in prothrombin time and plasma transaminase levels were mild and transient:

	SGOT*	SGPT*	PT %
Before isch.			
60	37±8	45±8	88±6
90	33±4	47±7	89±7
120	43±2	49±5	69±7
30 min after revasc.			
60	43±8	392±8	32±7
90	38±3	286±57	42±7
120	73±28	1205±478	51±9
3rd day postop.			
60	70±5	82±5	97±3
90	52±7	57±16	95±2
120	84±32	93±30	74±4

60, 90, 120 = duration of ischaemia (min).
Isch, Ischaemia; revasc., revascularization.
PT, Prothrombin time.
Values are mean±1 s.d.
* Normal <40 μ/ml.

No substantial pathological changes were observed on early (20 min) or late (1 month and 3 months in one case) liver specimens.

We conclude that pigs tolerate 2 h hepatic normothermic ischaemia provided that splanchnic venous pooling is prevented. Since splanchnic venous distension is well tolerated in humans, one can thus understand why portal triad occlusion is safe far beyond 15 min in humans. The myth of the high sensitivity of the liver to warm ischaemia should be revised.

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124. Successful prolongation of canine pancreas allografts with cyclosporin A

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Human pancreas allografts usually fail because of exocrine leakage and infection or because of pancreatic rejection. The prevention of pancreatic rejection by steroids is not ideal in an operation usually undertaken to improve carbohydrate control.

Cyclosporin A (CyA) is a non-steroid fungal metabolite which is an effective immunosuppressive agent in organ allografts in animals (Calne and White, 1977) and encouraging pilot studies with CyA have been reported in kidney allografts in man.

This study was undertaken to assess the effectiveness of CyA alone in delaying rejection of animals undergoing whole organ pancreas transplantation.

Forty-nine mongrel dogs were divided into 5 groups. Group 1 underwent total pancreatectomy alone. In the remaining groups total pancreatectomy was followed by whole organ pancreas allografts, placed orthotopically (18 animals) or heterotopically (26 animals) with pancreatic duct to ureter drainage. Group 2, no immunosuppressive treatment; group 3 received prednisolone 0·5 mg kg^{-1} d^{-1} and azothioprine 3 mg kg^{-1} d^{-1}. Group 4 received CyA 10 mg k^{-1} d^{-1} and group 5, CyA 25 mg kg^{-1} d^{-1}.

Technical complications with vascular thrombosis or pancreatitis occurred frequently and below are reported the results of animals surviving longer than 72 h.

Group	No.	Period of normoglycaemia (d)	Survival (median)
1	5	<1	13
2	3	4	20
3	7	9	23*
4	6	24	32
5	9	44	57**

Normoglycaemia = $<2\times$preop. blood sugar.
Mann–Whitney U test $*P = <0{\cdot}05$, $**P = <0{\cdot}01$.

CyA would appear on its own to prolong significantly the period of normoglycaemia after canine pancreas allografts.

CALNE R. Y. and WHITE D. J. G. (1977) Cyclosporin A, a powerful immunosuppressant in dogs with renal allografts. *IRCS Med. Sci.* **5**, 595.

CALNE R. Y., WHITE D. J. G., THIRUS S. et al. (1978) Cyclosporin A in patients receiving renal allografts from cadaver donors. *Lancet* **2**, 1323–1327.

125. A new method of non-invasive destruction of renal calculi by shock waves

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Until now, the lithotriptic destruction of renal calculi was accomplished by direct administration of ultrasound or electrohydraulic energy which is conducted by a catheter. However, this method can only be employed in cases of calculi of the urinary bladder or of the lower part of the ureter. Concrements of the renal pelvis are inaccessible by this technique. Besides, catheterization of the ureter is unpleasant and not without side effects.

The technique to be reported here is especially designed for the treatment of calculi of the renal pelvis, making catheterization of the ureter unnecessary. It was developed in collaboration with the Dornier Company in Germany. The principle, which has been successfully tested already in animal experiments, is disintegration of the concrement by energetic shock waves. The shock waves are generated outside of the body by underwater discharge of a condenser with the sparking electrodes localized in one focus of an elliptic cavity and have an amplitude >1 kbar and duration <1 μs. The shock waves formed are reflected at the concrement which is positioned in the other focus of the ellipse. The renal calculus, like any material of density very different from the wave conducting medium, is exposed to powerful tear and compressive forces, resulting in abrupt disintegration into small pieces, or even into small grains. However, the technique of precise localization of the renal concrement within the abdomen and subsequent positioning into focus opposite to the discharge electrodes, proved to be a formidable problem. This difficulty could be solved by employment of a two-dimensional X-ray scan which intersects in the second focus of the ellipsoid. Prior to administration, an affected patient is subjected to several reciprocative movements and manoeuvres over the ellipsoid until the renal concrement is exactly in target (i.e. second focus). Subsequently, one or several spark discharges are triggered until the calculus has disintegrated. This can be controlled by an X-ray monitor.

Until now, the technique has been tested in 60 mongrel dogs, where during previous operations renal calculi of different magnitude and consistency obtained from humans had been implanted into the renal pelvis. In any case where the concrement could be correctly moved into target position, disintegration on exposure was accomplished which was followed by subsequent excretion via the urinary tract. Damage to surrounding tissues was never observed. Only if shock waves strike on matter of very different density relative to the medium, as for example air-containing lung tissue, rupturing of tissue may occur. On the other hand, passage of shock waves through tissue containing fluid does not cause any damage as demonstrated in many experiments with tissue culture, blood samples or small animals in total. Currently, the equipment initially developed for experimentation in dogs is being adapted for human purposes because in a great number of different animal studies no evidence was obtained that non-invasive concrement destruction by shock waves should not be used in man.

126. Plasma heparin levels and operative blood loss after intrapulmonary heparin

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127. The nature of insulin resistance in sepsis

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The role of 'insulin resistance' in the metabolic abnormalities of severe sepsis was studied by correlation of clinical observations and animal experiments.

Fourteen patients (none in shock) with peritonitis or abscesses who fasted for 8 h were compared with 9 normal people who fasted overnight. The uptake or release of substrates, metabolites and amino acids (AA) by peripheral tissues were measured by femoral A – V differences and leg blood flow (dye dilution) (*Table I*).

In sepsis both blood glucose and insulin are elevated. However, the metabolic defect does not lie in insulin binding, glucose transport, or glycogen synthesis. Rather, 'insulin resistance' appears to be an inability in muscle to induce PDH and to increase oxidation of glucose. Associated are accelerated proteolysis, consumption of branch chain AA, release of glucogenic AA and lactate.

Table I: LEG UPTAKE OR RELEASE AND ARTERIAL BLOOD CONCENTRATION (mean±s.d.)

	Normal ($n = 9$)	Septic ($n = 14$)	Septic/normal
Blood insulin (U/l)	21±5	38±8	180%
Glucose uptake (μmol/m^2/min)	18±2	122±31	670%
Lactate release (μmol/m^2/min)	−17±4	−42±7	247%
FFA uptake (μmol/m^2/min)	24±7	7±5	29%
Selected amino acids release:			
Alanine	−9±3	−42±4	455%
Leucine	−2±2	−9±2	451%
Tyrosine	−0·6±1	−3±1	481%

The incubated soleus muscles of 3-day fasted normal 70-g rats were compared with those of septic fasted animals 3 days after caecal ligation (*Table II*).

Table II: INCUBATED SOLEUS MUSCLE

	Normal	Septic	Septic/normal
Blood insulin (U/l)	15 ($n = 16$)	27 ($n = 21$)	180±10%
Insulin binding at 6 mol insulin conc. (fmol/mg muscle)	3·53 ($n = 52$)	3·95 ($n = 56$)	112±29%
C-14 Deoxyglucose uptake (pmol/mg muscle)	67 ($n = 18$)	110 ($n = 17$)	164±92%
C-14 Glycogen synthesis (μmol glucose converted to glycogen mg^{-1} h^{-1})	6·6 ($n = 19$)	10·6 ($n = 20$)	161±28%
C-14 Carbon dioxide production from 14C(U) glucose (nmol mg^{-1} h^{-1})	5·63 ($n = 12$)	6·19 ($n = 19$)	110±8%

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128. Evidence of immunophagocytic potential within the central nervous system

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The primary biological function of normal glial tissue, which constitutes up to 60 per cent of the human brain, remains unclear. While the mesodermal microglia cell is an important scavenger cell within the CNS none of the other ectodermal glial constituents are known to be lymphoid in origin and the brain lacks both a lymphoid organ analogous to the lymph node and a conventional afferent and efferent lymphatic system.

We found an absence of T lymphocytes, as measured by E rosetting, in all suspensions of normal brain and in 9 of 10 suspensions of brain tumours we examined. In contrast, using ox red blood cell rosettes with various antisera, we consistently found Ig, Fc and C3 surface membrane receptors on a remarkably high percentage of normal glia and astrocytoma cells. These latter findings are new. Similar markers are normally confined to immunophagocytic cells of the lymphoid system and possibly tumour cells (Eremin et al., 1976). While a classic T lymphocytic cell mediated response can occur within the brain, subject to an adequate antigenic stimulus and possibly breach of the blood–brain barrier, our experiments confirm this is rare in tumours and point to an additional immunophagocytic potential or surveillance role for macroglia, as well as for microglia, within the central nervous system.

EREMIN O., PLUMB D. and COOMBS R. R. A. (1976) T and B lymphocyte populations in human normal lymph node, regional tumour lymph node and inflammatory lymph node. *Int. Arch. Allergy Appl. Immunol.* **52**, 277–290.

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129. Adjuvant cytotoxic liver perfusion for colorectal cancer

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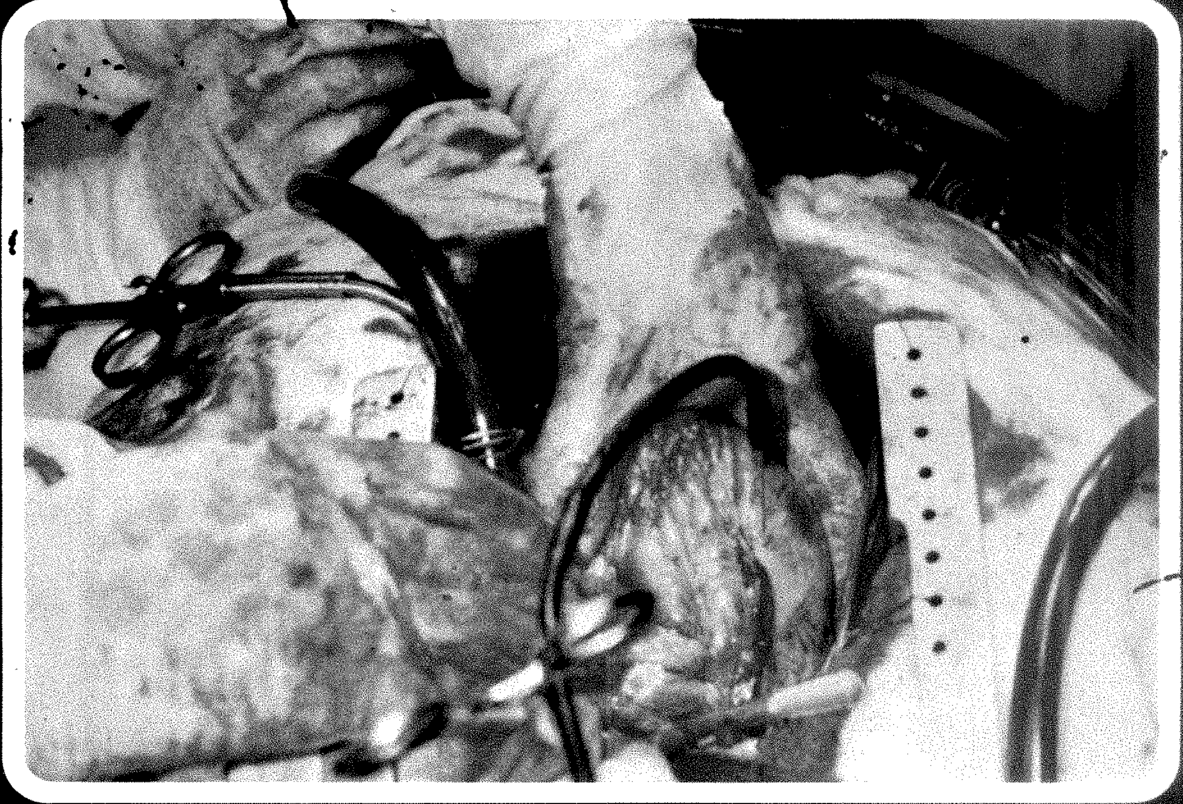

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1 Brit med J (1978), **1**, 1603
2 Thorax (1978), 33, **1**, 130
3 Brit med J (1978), **2**, 536
4. Brit. med. J (1970), **4**, 455
5. Zbl. Bakt Hyg., I Abt Orig A (1976), **236**, 235

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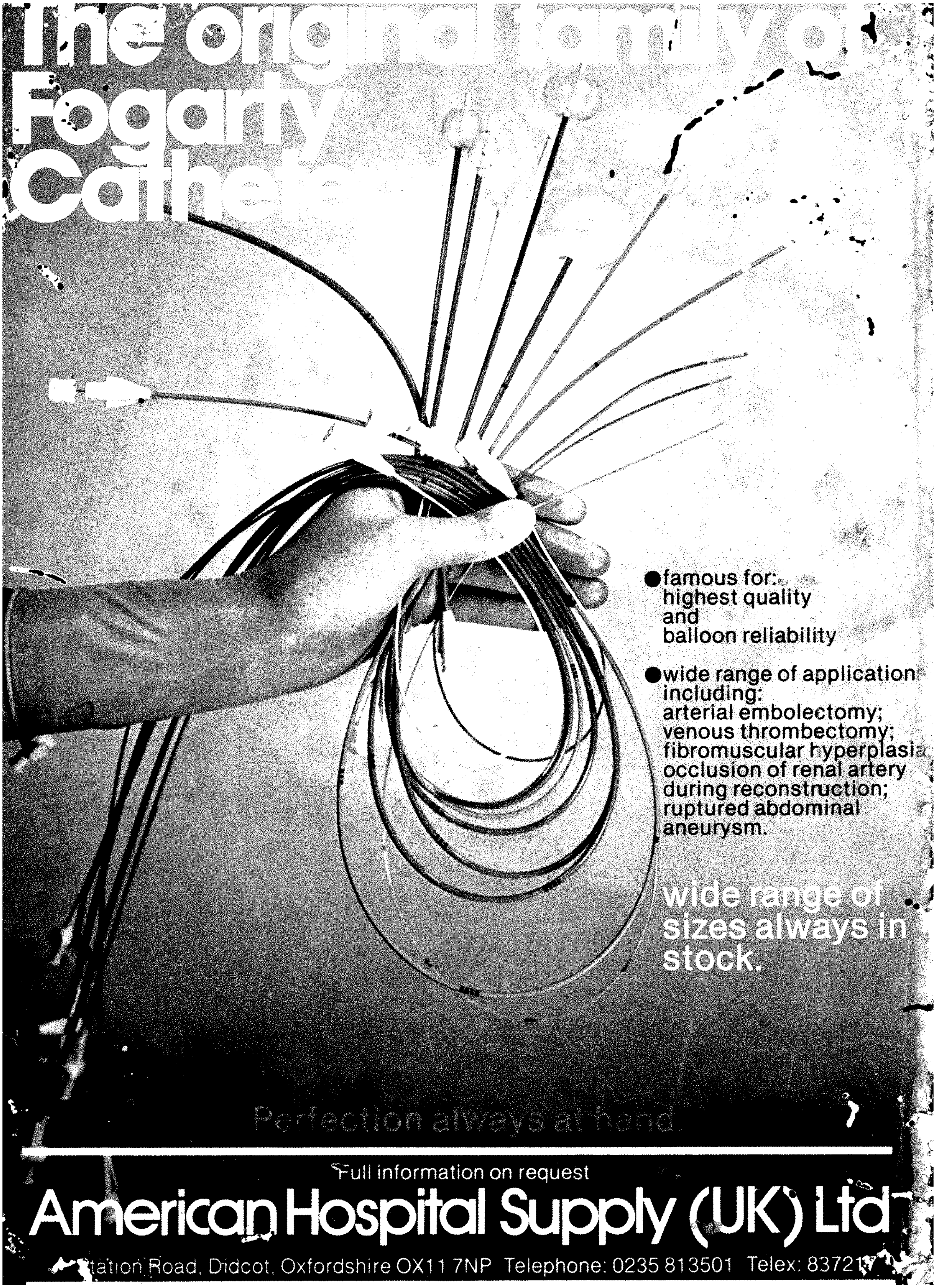

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